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(54) Title: AMINOINDAZOLE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

(57) Abstract: Compounds which are indazole derivatives and pharmaceutically acceptable salts thereof together with pharmaceutical compositions comprising them, as well as combinatorial libraries of indazole derivatives, as set forth in the specification, are disclosed; these compounds or compositions may be useful in the treatment of diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

TITLE OF THE INVENTION

AMINOINDAZOLE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM.

BACKGROUND OF THE INVENTION

Field of the invention

The present invention relates to aminoindazole derivatives active as kinase inhibitors and, more in particular, it relates to 3-aminoindazoles and derivatives thereof, to a process for their preparation, to pharmaceutical compositions comprising them and to their use as therapeutic agents, particularly in the treatment of diseases linked to disregulated protein kinases.

Discussion of background

The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases. A large share of the oncogenes and proto-oncogenes involved in human cancers code for PKs. The enhanced activities of PKs are also implicated in many non-malignant diseases, such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. PKs are also implicated in inflammatory conditions and in the multiplication of viruses and parasites. PKs may also play a major role in the pathogenesis and development of neurodegenerative disorders.

For a general reference to PKs malfunctioning or disregulation see, for instance, Current Opinion in Chemical Biology 1999, 3, 459 - 465.

SUMMARY OF THE INVENTION

It is an object of the invention to provide compounds which are useful in therapy as agents against a host of diseases caused by and/or associated to a disregulated protein kinase activity.

It is another object to provide compounds which are endowed with multiple protein kinase inhibiting activity.

The present inventors have now discovered that the compounds of the invention, hereinafter shortly referred to as aminoindazole derivatives, are endowed with multiple protein kinase inhibiting activity and are thus useful in therapy in the treatment of diseases associated with disregulated protein kinases.

More specifically, the compounds of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of PKs in the regulation of cellular proliferation, these compounds are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

The compounds of the invention can be useful in the treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (*J. Biochem.*, 117, 741-749, 1995).

The compounds of this invention, as modulators of apoptosis, may also be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorders.

The compounds of this invention may be useful in inhibiting tumor angiogenesis and metastasis.

The compounds of the invention are useful as cyclin dependent kinase (cdk) inhibitors and also as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases.

DETAILED DESCRIPTION OF THE INVENTION

Several indazoles and aminoindazoles are known in the art as synthetic or chemical intermediates, as polymer stabilizers, as therapeutic agents and even as protein kinase inhibitors.

As an example, some alkylamino-indazoles are disclosed in US 28939 (reissue of US 3,133,081) by Smithkline Co., as endowed with muscle relaxant and analgesic activity; among them are 3-methylamino-5-trifluoromethyl-indazole and 3-diethylamino-5-trifluoromethyl-indazole.

Cyclic N,N'-urea derivatives bearing 3-aminoindazole groups are disclosed in Bioorg. Med. Chem. Lett. (1998), 8(7), 715-720 as HIV protease inhibitors.

Diaryl-urea derivatives are disclosed either as p38 kinase inhibitors useful in the treatment of diseases other than cancer, as well as for treating cancerous cell growth mediated by RAF kinase, in WO 99/32111 and WO 99/32106 by Bayer Co; among the compounds specifically exemplified therein is N-[4-[(pyridyl-4-yl)oxy]phenyl]-N'-[6-chloro-(indazol-3-yl)]-urea.

Imidazopyridine derivatives further substituted by aryl moieties, e.g. by indazolyl-aminocarbonyl-phenyl, are disclosed as platelet-activating factor (PAF) antagonists in WO 91/17162 by Pfizer Ltd.

Indazole compounds further substituted in position 3 by groups other than amino or derivatives thereof are disclosed in WO 01/02369 by Agouron Pharmaceuticals Inc., as possessing protein kinase inhibitory activity.

Mercapto-cyanoacryloylamino- or alkylthio-cyanoacryloyl-amino-heterocycles are discloses as being useful in the treatment of disorders associated with increased cell growth in US 5,714,514 by Hoechst.

1-Acylamino-3-(N-arylsulfonyl-N-alkoxyamino)-2-hydroxy-

propane derivatives, wherein the aryl moiety also comprises indazole groups, are disclosed as HIV aspartyl protease inhibitors in WO 99/65870 by Vertex Pharmaceuticals Inc.

Quinolylamino- and quinazolylamino-indazoles are disclosed in WO 97/03069 by Glaxo Group Ltd. as possessing protein tyrosine kinase inhibitory activity.

Arylamino-indazoles further substituted in position 5 by heterocyclic rings are disclosed in WO 95/28400 by Glaxo Group Ltd. as possessing selective 5-HT1 agonist activity; the said compounds are thus reported to be useful in the treatment of migraine.

Some other specific indazole derivatives are known as therapeutic agents: in particular, 3-[3-(morpholin-4-yl)propionylamino]-indazole, 3-(N,N,-diethylamino)-propylamino-5-methoxy-indazole, 3-[(3-methyl)morpholin-4-yl]-propylamino-5-methoxy-indazole 3-(N,N,-diethylamino)-propylamino-5-methyl-indazole and 3-[(3-methyl)morpholin-4-yl]-propylamino-5-methyl-indazole are disclosed as possessing analgesic and anti-inflammatory activity [see US 4,751,302 and JP-A-60061569 by Asahi Chemical Industry]; 3-[(2-hydroxyphenyl)carbonylamino]-indazole is disclosed as antimicrobial agent [see Pharmazie (1990), 45(6), 441-2].

Several other indazoles, mainly disclosed as chemical intermediates or for purposes other than therapeutic, e.g. polymer stabilizers, bleaching agents, dyes and the like, are known in the art.

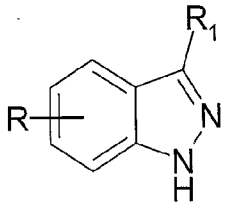
Among them are: 3-(ethoxycarbonylamino)-indazole [see Chemical Abstracts 92(1980):215400]; 3-acetylamino-indazole and 3-benzoylamino-indazole [see J. Org. Chem.(1996), 61(24), 8397-8401]; 3-butyrylamino-indazole, 3-[(4-chlorophenyl)carbonylamino]-indazole, 3-[(4-methyl-phenyl)carbonylamino]indazole and 3-[(3,3-diphenyl)propionylamino]indazole [see Acta Chim. Hung. (1990), 127(6), 795-802]; 3-[(3,5-dimethyl-isoxazol-4-yl)carbonylamino]-indazole [see J. Heterocyl. Chem. (1974), 11(4), 623-6]; 3-[(4-nitrophenyl)carbonylamino]-indazole and 3-(phenylacetylamino)-indazole [see J. Chem. Soc., Perkin Trans. 1 (1982), (3), 759-66]; 3-[(2-aminophenyl)carbonylamino]-indazole and 3-[(2-nitrophenyl)carbonylamino]-indazole [Heterocyles (1996), 43(11), 2385-2396]; 3-[(4-chloro-2-nitrophenyl)carbonyl-amino]-indazole, 3-[(2-amino-4-chlorophenyl)carbonylamino]-indazole, 3-[(2-amino-5-chlorophenyl)carbonylamino]-

indazole and 3-[(3-chloro-6-nitrophenyl)carbonylamino]-indazole [see Arch. Pharm. (1999), 332 (9), 317-320]; 3-(acetylamino)-5-amino-indazole [see US 3,316,207 by Farbwerke Hoechst A.G.]; 3-dimethylamino-5-trfifluoromethyl-indazole [see DE-A-2458965 by Bayer A.G.]; 3-phenylamino-6-methyl-indazole, 3-phenylamino-, 3-(4-chloro)phenylamino-, 3-(4-methyl)phenylamino-, 3-(3-methyl)phenylamino- and 3-(4-aminosulfonyl)phenylamino-5-methyl-indazole [see Chemical Abstracts 78(1973):136158]; 3-[(1-hydroxy-2-methyl)-2-propyl]amino-6,7-dimethoxy-indazole [see US 4,864,032 by Ortho Pharmaceutical Co.].

Sulfonylaminoindazoles and, more particularly, long chain alkyloxyphenylsulfonylamino-indazoles are disclosed as cyan dye forming compounds in JP-A-08022109, by Heisei.

In addition, 3-aminoindazole derivatives, either unsubstituted or substituted at the phenyl moiety by alkoxy, aryloxy, arylaklyoxy groups and the like, are disclosed as protein kinase inhibitors in the co-pending US patent application No. 09/962162 (filed in September 26, 2001, in the name of Pharmacia & Upjohn S.p.A.) which is herewith incorporated by reference.

Accordingly, the present invention provides a method for treating diseases caused by and/or associated with an altered protein kinase activity, by administering to a mammal in need thereof an effective amount of a compound represented by formula (I)



(I)

wherein

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heteroatoms selected from S, O and N;

$\mathbf{R_1}$ is an optionally substituted group selected from

-N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

$\mathbf{R_a}$ and $\mathbf{R_b}$ are, each independently, hydrogen or a straight or branched C_1-C_6 alkyl group;

R' and **R"** are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or

cycloalkyl C_1-C_6 alkyl, aryl or aryl C_1-C_6 alkyl wherein aryl is as above defined;, or a 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl; or, when taken together with the nitrogen atom to which they are attached, R' and R" may form an optionally substituted 4 to 7 membered heterocycle, optionally containing an additional heteroatom selected from S, O or N;

or isomers, tautomers, carriers, prodrugs, and pharmaceutically acceptable salts thereof.

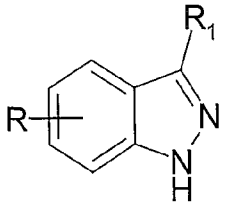
In a preferred embodiment of the method described above, the disease caused by and/or associated with an altered protein kinase activity is selected from the group consisting of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Specific types of cancer that may be treated include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

In another preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

In addition, the method object of the present invention, also provides tumor angiogenesis and metastasis inhibition.

The present invention further provides a compound represented by formula (I)



(I)

wherein

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heteroatoms selected from S, O and N;

$\mathbf{R_1}$ is an optionally substituted group selected from

-N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

$\mathbf{R_a}$ and $\mathbf{R_b}$ are, each independently, hydrogen or a straight or branched C_1-C_6 alkyl group;

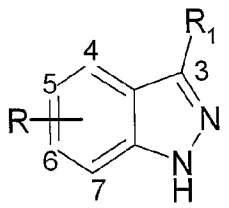
R' and **R"** are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl or aryl C_1-C_6 alkyl wherein aryl is as above defined, or a 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl; or, when taken together with the nitrogen atom to which they are attached, R' and R" may form an optionally substituted 4 to 7 membered heterocycle, optionally containing an additional heteroatom selected from S, O or N;

or isomers, tautomers, carriers, prodrugs, and pharmaceutically acceptable salts thereof.

Unless otherwise specified, when referring to the compounds of formula (I) per se as well as to any pharmaceutical composition thereof or to any therapeutic method of treatment comprising them, the present invention includes all of the hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which release the active parent drug according to formula (I) in vivo.

If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture or as an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

In the present description, as formerly indicated, R is in position 5 or 6 of the indazole group, according to the following numbering system:



(I)

In the present description, unless otherwise specified, with the term halogen atom we intend a fluorine, chlorine, bromine or iodine atom.

With the term straight or branched C_1-C_6 alkyl group we intend any group such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, and the like.

With the term C_2-C_6 alkenyl or alkynyl group we intend any of the aforementioned straight or branched alkyl groups, with from 2 to 6 carbon atoms, further bearing a double or triple bond. Non limiting examples of alkenyl or alkynyl groups of the invention are, for instance, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 1-hexenyl, ethynyl, 2-propynyl, 4-pentynyl, and the like.

With the term C_3-C_6 cycloalkyl we intend, unless otherwise indicated, any 3 to 6 membered carbocyclic ring such as, for instance, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

With the term aryl we intend a mono-, bi- or poly- either carbocyclic as well as heterocyclic hydrocarbon with from 1 to 4 ring moieties, either fused or linked to each other by single bonds, wherein at least one of the carbocyclic or heterocyclic rings is aromatic.

From the above it is clear to the skilled person that, whereas any aryl group with 0 heteroatoms is an aromatic carbocyclic ring, any aryl group with from 1 to 3 heteroatoms is an aromatic heterocyclic ring, also known as heteroaryl group.

Unless otherwise specified, the said heteroaryl groups are 5 or 6 membered rings with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulphur.

Non limiting examples of aryl groups of the invention are, for instance, phenyl, indanyl, biphenyl, α- or β-naphthyl, fluorenyl, 9,10-dihydroanthracenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, imidazopyridyl, 1,2-methylenedioxyphenyl, thiazolyl, isothiazolyl, pyrrolyl, pyrrolyl-phenyl, furyl, phenyl-furyl,

benzotetrahydrofuranyl, oxazolyl, isoxazolyl, pyrazolyl, chromenyl, thienyl, benzothienyl, isoindolinyl, benzoimidazolyl, isoindolinyl-phenyl, quinolinyl, isoquinolinyl, 2,6-diphenyl-pyridyl, quinoxalinyl, pyrazinyl, phenyl-quinolinyl, benzofurazanyl, 1,2,3-triazolyl, 1-phenyl-1,2,3-triazolyl, and the like.

With the term 5 or 6 membered heterocyclyl, hence encompassing aromatic heterocyclic groups also referred to as aryl groups, we further intend a saturated or partially unsaturated 5 or 6 membered heterocycle with from 1 to 3 heteroatoms such as nitrogen, oxygen and sulfur.

Examples of these 5 or 6 membered heterocyclyl groups, optionally benzocondensed or further substituted, are 1,3-dioxolane, pyran, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, tetrahydrofuran, and the like.

When referring to the compounds of formula (I) wherein R_1 is a group -NHCONR'R" and R' and R" are taken together with the nitrogen atom to which they are attached, they may also form an optionally substituted 4 to 7 membered heterocycle, optionally containing a heteroatom selected from S, O or N, in addition to the N atom directly bonded to R' and R".

For a general reference to the above heterocyclic groups see, for instance, cyclic amino derivatives per the following table VI.

From all of the above, it is clear to the skilled man that any group which name has been identified as a composite name such as, for instance, cycloalkylalkyl, arylalkyl, heterocyclylalkyl and the like, has to be intended as conventionally construed from the parts to which it derives. So far, the term heterocyclyl-alkyl stands for a straight or branched alkyl group being further substituted by a heterocyclyl group, as above defined.

According to the above meanings provided to R, R_1, R' and, R", any of the above groups may be further optionally substituted in any of their free positions by one or more groups, for instance 1 to 6 groups, selected from: halogen, nitro, oxo groups (=O), carboxy, cyano, alkyl, perfluorinated alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, amino groups and derivatives thereof such as, for instance, alkylamino, dialkylamino, arylamino, diarylamino, ureido, alkylureido or arylureido; carbonylamino groups and derivatives thereof such as, for instance, formylamino, alkylcarbonylamino,

alkenylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino; hydroxy groups and derivatives thereof such as, for instance, alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy or alkylideneaminooxy; carbonyl groups and derivatives thereof such as, for instance, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl; sulfurated derivatives such as, for instance, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, arylsulfonyloxy, aminosulfonyl, alkylaminosulfonyl or dialkylaminosulfonyl.

In their turn, whenever appropriate, each of the above substituents may be further substituted by one or more of the aforementioned groups.

The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the present invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, trifluoroacetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, phydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of the present invention by reacting, for example, the appropriate acid or base.

A first embodiment of the invention is represented by the derivatives of formula (I) wherein R is an optionally substituted aryl group and R_1 is a group -NHCOR', wherein R' is as above defined.

Another embodiment of the invention is represented by the derivatives of formula (I) wherein R is an optionally substituted aryl group and R_1 is a group -NHCONR'R", wherein one of R' or R" is a hydrogen atom and the remaining one of R' or R" is as above defined.

Another embodiment of the invention is represented by the derivatives of formula (I) wherein R is an optionally substituted aryl group and R_1 is a group -NHCONR'R", wherein R' and R" are both, as above defined, other than hydrogen.

Another embodiment of the invention is represented by the derivatives of formula (I) wherein R is in optionally substituted aryl group and R_1 is a group $-NHSO_2R'$, wherein R' is as above defined.

Another embodiment of the invention is represented by the derivatives of formula (I) wherein R is in optionally substituted aryl group and R_1 is a group -NHCOOR', wherein R' is as above defined.

Another embodiment of the invention is represented by the derivatives of formula (I) wherein R is in optionally substituted aryl group and R_1 is a group $-N=CH-NR_aR_b$, wherein R_a and R_b are both methyl groups.

Preferably, in all of the above classes, the optionally substituted aryl group, in position 5 or 6 of the indazole ring, is selected from any 5 or 6 membered aryl group with from 0 to 3 heteroatoms selected among N, O or S, optionally further benzocondensed.

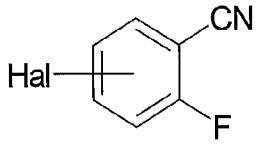
Typical examples of preferred aryl groups of the invention are, for instance, phenyl, biphenyl, α- or β-naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, thiazolyl, isothiazolyl, pyrrolyl, furyl, benzofuranyl, oxazolyl, isoxazolyl, pyrazolyl, thienyl, benzothienyl, benzoimidazolyl, quinolinyl, isoquinolinyl, and the like.

Specific examples of compounds of formula (I), optionally in the form of pharmaceutically acceptable salts, are conveniently listed in the experimental section and claims.

As set forth above, it is a further object of the present invention a process for preparing the compounds of formula (I).

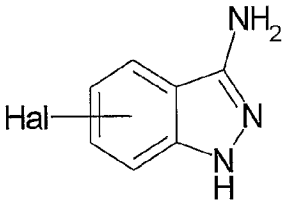
Therefore, the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be obtained by a process comprising:

a) reacting a compound of formula (II) with hydrazine hydrate



(II)

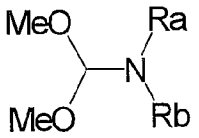
wherein Hal is a halogen atom, so as to obtain a compound of formula (III)



(III)

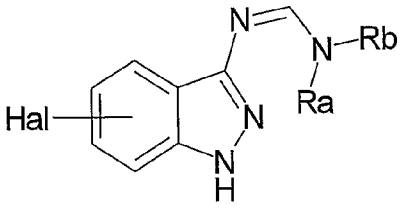
wherein the halogen atom is in position 5 or 6 of the indazole ring;

b) reacting the compound of formula (III) with a suitable dimethylacetal derivative of formula (IV)



(IV)

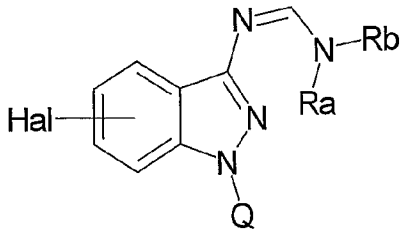
wherein R_a and R_b are as above defined, so as to obtain a compound of formula (I)



(I)

wherein R_a and R_b are as above defined; and, optionally, converting the thus obtained compound of formula (I) into another compound of formula (I), by:

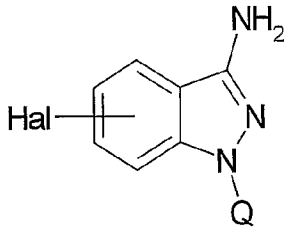
c) reacting the compound of formula (I), as per step (b) of the process, with a suitable indazole nitrogen protecting agent or, alternatively, supporting it onto a suitable polymeric resin so as to obtain a compound of formula (V)



(V)

wherein Q is the above nitrogen protecting group or represents the supporting resin;

d) reacting the compound of formula (V) with hydrazine monohydrate so as to get a compound of formula (VI)

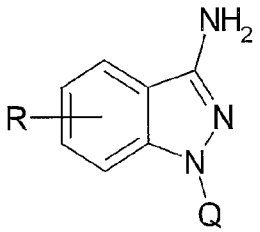


(VI)

e) reacting the compound of formula (VI) with a suitable boronic acid derivative of formula (VII)

$$R\text{-}B(OH)_2 \quad (VII)$$

wherein R is as above defined, so as to obtain a compound of formula (VIII)



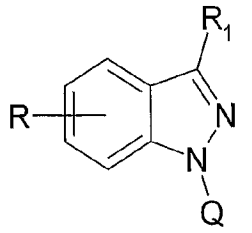
(VIII)

and reacting the compound of formula (VIII) according to any one of the alternative steps (f.1) or (f.2), as follows:

f.1) with any one of the compounds of formula (IX), (X), (XI) or (XII)

$$R'CO\text{-}Z \quad (IX) \qquad R'SO_2\text{-}Z \quad (X) \qquad R'\text{-}NCO \quad (XI) \qquad R'OCO\text{-}Z \quad (XII)$$

wherein R' is as above defined and Z is a halogen atom or a suitable leaving group, so as to obtain the compounds of formula

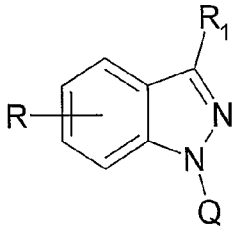

(XIII)

wherein R and Q are as above defined and R_1 is a group -NHCOR', $-NHSO_2R'$, -NHCONHR' or -NHCOOR'; or

f.2) with a suitable amine of formula (XIV)

HNR'R" (XIV)

wherein R' and R" are as above defined, in the presence of a suitable aryl chloroformate derivative, so as to obtain a compound of formula (XIII)


(XIII)

wherein R and Q are as above defined and R_1 is a group of formula -NHCONR'R";

g) deprotecting the compound of formula (XIII) being obtained according to any one of steps (f.1) or (f.2) or, alternatively, cleaving the polymeric resin so as to get the desired compound of formula (I) and, whenever desired, converting it into another compound of formula (I) and/or into a pharmaceutically acceptable salt thereof.

From all of the above, it is clear to the person skilled in the art that if a compound of formula (I), prepared according to the above process, is obtained as an admixture of isomers, their separation into the single isomers of formula (I), carried out according to conventional techniques, is still within the scope of the present invention.

Likewise, the conversion into the free compound (I) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.

According to step (a) of the process, a compound of formula (II), preferably 4-bromo-2-fluorobenzonitrile or 5-bromo-2-fluorobenzonitrile, is reacted with hydrazine hydrate so as to get the formation of the indazole ring.

The reaction may be carried out according to conventional methods, for instance in a lower alcohol, preferably n-butanol, at a temperature ranging from room temperature to refluxing temperature, and for a time of about 4 to about 12 hours.

According to step (b) of the process, the compound of formula (I) having R_1 as a -N=CH-NR_aR_b group can be easily prepared by reacting the indazole derivative of formula (III) with a dimethylacetal derivative of formula (IV), for instance dimethylformamide dimethylacetal wherein R_a and R_b are both methyl groups.

The reaction is carried out according to conventional methods, by operating in a suitable solvent, for instance dimethylformamide, at room temperature and for a time varying from about 8 to about 36 hours.

According to step (c) of the process, the indazole derivative of formula (I) wherein R_1 is a -N=CH-NR_aR_b group is either protected at the indazole nitrogen atom or, alternatively, is supported onto a suitable polymeric resin.

The reaction of protection may be carried out according to conventional methods well known in the art, for instance by using suitable nitrogen protecting groups such as, for instance, tert-butoxy-carbonyl (BOC) group.

At this same position, in the alternative, this indazole derivative may be also conveniently anchored to an inert polymeric support such as, for instance, the 2-chloro-trityl chloride resin, the trityl chloride resin, the p-nitrophenyl carbonate Wang resin or the bromo-(4-methoxyphenyl)methyl polystyrene, which are all conventionally known in this field.

Clearly, this same option is particularly advantageous for preparing the compounds of formula (I) under solid-phase-synthesis (SPS) conditions, which are typically adopted when preparing libraries of compounds according to combinatorial chemistry techniques, for instance as reported below.

The reaction with the resin is carried out in the presence of a slight excess of a suitable base, for instance an amine, e.g. diisopropylethylamine (DIPEA), triethylamine (TEA), 1,8-diazabiciclo[5.4.0]undec-7-ene (DBU) or 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, in a suitable solvent, for instance dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, dimethylacetamide, 1-methyl-2-pyrrolidinone and the like.

Preferably, the reaction is carried out in 1-methyl-2-pyrrolidinone at a temperature of about 20°C.

The reaction may be performed by adding to a suspension of the resin, the base and the indazole derivative, and by stirring at a temperature of about 20°C for a suitable time, for instance up to 24 hours.

According to step (d) of the process, the protected- or otherwise polymer supported-derivative of formula (V) is reacted with hydrazine monohydrate in a suitable solvent, for instance water, pyridine and admixtures thereof. Preferably, the reaction is carried out in the presence of pyridine/water admixtures, at a temperature ranging from about 40°C to about 100°C and for a suitable time, for instance from 24 hours to few days, e.g. 48 hours.

According to step (e) of the process, the 3-amino-indazole derivatives of formula (VI) are then reacted with a suitable boronic acid of formula (VII), according to well-known Suzuki coupling conditions.

Typically, the reaction is carried out in the presence of catalytic amounts of tris(dibenzylideneacetone)dipalladium, palladium acetate, 1,1'-bis(diphenylphosphino)ferrocene-dichloropalladium, tetrakis(triphenylphosphine)palladium or bis(triphenylphosphine)palladium chloride. The reaction occurs by adding a suitable base, for instance cesium carbonate, potassium phosphate tribasic and the like, and a palladium ligand, for instance triphenylphosphine.

In this respect, the compound of formula (VI) is suspended in a suitable degased solvent such as toluene, N-methyl-2-pyrrolidone, dimethoxyethane, dioxane, and the like; a mixture of water and dimethoxyethane being preferred.

Subsequently, the compound of formula (VII), the catalyst, the base and the ligand are then added therein. The suspension is then brought to a suitable temperature varying from about 50°C to about 100°C whereas stirring is maintained for a time of about 8 hours to few days e.g. 48 hrs. The reaction is carried out under inert atmosphere.

The indazole derivative of formula (VIII) thus prepared can be then conveniently reacted according to any one of the alternative steps (f.1) or (f.2).

As per step (f.1) of the process, the compound of formula (VIII) is reacted with a suitable reagent of formula (IX), (X), (XI) or (XII), according to well-known methods.

Typically, the compound of formula (VIII) may be reacted with: a compound of formula (IX) so as to get the corresponding amido derivative wherein R_1 is a group -NHCOR' and R' is as above defined; a compound of formula (X) to get the corresponding sulfonamido derivative wherein R_1 is a group $-NHSO_2R'$ and R' is as above defined; a compound of formula (XI) to get the corresponding ureido derivative wherein R_1 is a -NHCONHR' group and R' is as above defined; with a compound of formula (XII) to get the corresponding carbamate derivative wherein R_1 is a -NHCOOR' group and R' is as above defined.

Any one of the above reactions is carried out according to conventional methods normally used in the preparation of functionalized amino derivatives, by starting from the corresponding amine.

Preferably, within the compounds of formula (IX), (X) or (XII), Z represents a halogen atom and, even more preferably, a chlorine atom.

In this respect, the compound of formula (VIII) is dissolved in a suitable solvent such as dichloromethane, chloroform, dimethylformamide, tetrahydrofuran, dioxane, pyridine and admixtures thereof, and a suitable base is added such as, for instance, triethylamine, diisopropylethylamine, sodium carbonate, 1-methyl-imidazole, and the like. The compound of general formula (IX), (X) or (XII) is then added and the mixture stirred for a time of about 2 hours to about 24 hours, at a temperature ranging from about 20°C to about 50°C. In all of these reactions, a suitable catalyst such as dimethylamino pyridine may be optionally used.

Preferably, when the reaction is performed in the presence of a reagent of general formula (IX) or (X), a further treatment with ammonium hydroxide is required so as to remove any side product being formed.

When using an isocyanate of general formula (XI), the reaction conditions are those as above reported, with the exception that the base may not be required.

Alternatively, as per step (f.2) of the process, the compound of formula (VIII) may be reacted with a compound of formula R'R"NH (XIV), in the presence of a suitable aryl

chloroformate, for instance 4-nitrophenyl- or 4-chlorophenyl-chloroformate so as to get the corresponding ureido –NHCONR'R" derivative of formula (XIII).

As an example, to the compound of formula (VIII) properly dissolved in a suitable solvent such as dichloromethane, chloroform, dimethylformamide, tetrahydrofuran, dioxane and admixtures thereof, a suitable base such as triethylamine, diisopropylethylamine, sodium carbonate, 1-methyl imidazole and the like, together with a suitable aryl chloroformate, for instance 4-nitrophenyl- or 4-chlorophenyl-chloroformate, are added therein. The mixture is stirred for about 1 hour to about 12 hours at room temperature. The compound of formula (XIV) is then added to this suspension, and the mixture is stirred from about 12 hours to about few days, at a temperature ranging from about 20°C to about 40°C.

Finally, according to step (g) of the process, the compound of formula (XIII) is deprotected at the indazole nitrogen atom by working according to conventional methods, in acidic conditions. The compound of formula (XIII) is thus suspended in a suitable solvent such as methyl alcohol, ethyl alcohol or the like, and a concentrated solution of hydrochloric acid is added. The mixture is stirred for a suitable time of about 5 hours to about 15 hours at a temperature ranging from about 20°C to about 40°C; preferably at about 20°C.

Alternatively, this same intermediate compound of formula (XIII) is cleaved from the resin to which it is supported.

Resin cleavage may be carried out, for instance, in the presence of trifluoroacetic acid so as to yield the desired compound of formula (I). The resin is suspended in a solution of 5-95% of trifluoroacetic acid in dichloromethane or chloroform and the mixture is stirred at about 20°C for a time varying from about 5 minutes to about 3 hours.

When preparing the compounds of formula (I) according to any variant of the process, which are all to be intended as within the scope of the present invention, optional functional groups within both the starting materials, the reagents or the intermediates thereof, and which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques.

Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

Pharmaceutically acceptable salts of the compounds of formula (I) or, alternatively, their free compounds from the salts thereof, my be all obtained according to conventional methods.

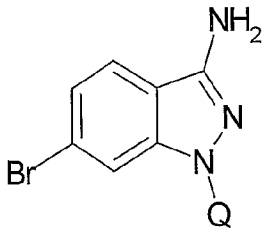
The starting materials of formula (II) of the above process are known and commercially available or, alternatively, may be prepared according to well-known methods.

Likewise, if not commercially available per se, the compounds of formula (IV), (VII), (IX), (X), (XI), (XII) and (XIV), are all known or easily prepared according to well-known methods.

As formerly indicated, the compounds of formula (I) of the invention were conveniently prepared according to combinatorial chemistry techniques widely known in the art, by accomplishing the aforementioned reactions between the intermediates in a serial manner and by working under SPS conditions.

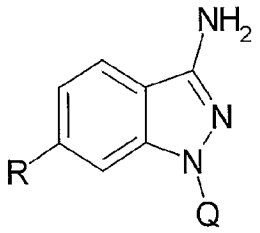
All of the preferred compounds of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, are herewith conveniently indicated and defined as products by process, that is as products of formula (I) which are obtainable, for instance through a given process.

Therefore, herewith provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIa)



(VIa)

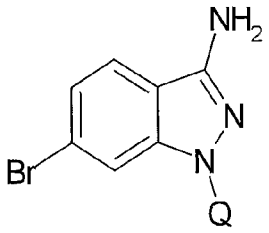
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

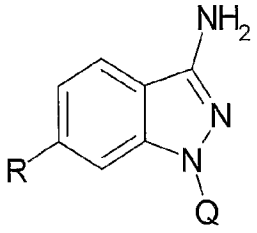
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (IX), as set forth in table II, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIa)



(VIa)

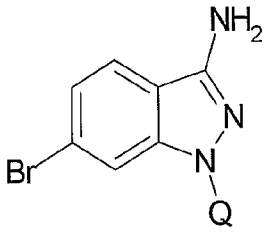
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

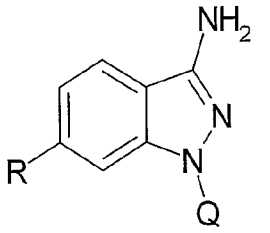
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (X), as set forth in table III, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIa)



(VIa)

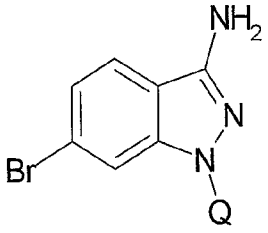
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

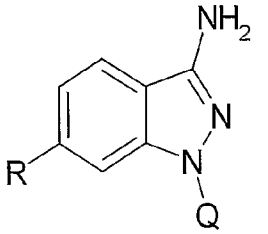
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (XI), as set forth in table IV, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIa)



(VIa)

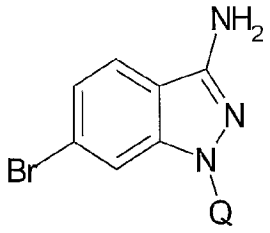
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

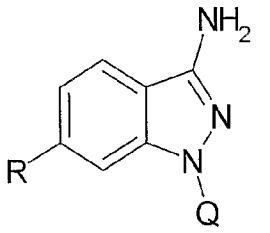
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (XII), as set forth in table V, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIa)



(VIa)

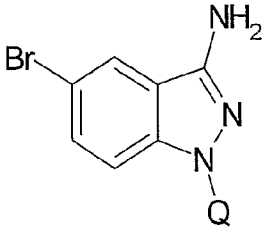
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

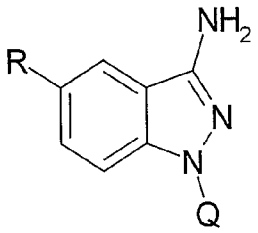
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (XIV), as set forth in table VI, in the presence of 4-nitrophenyl-chloroformate, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIb)



(VIb)

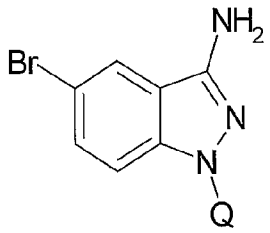
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

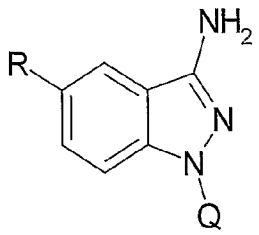
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (IX), as set forth in table II, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIb)



(VIb)

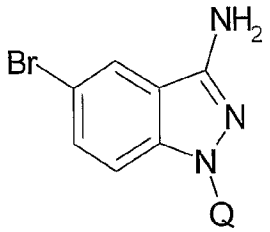
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

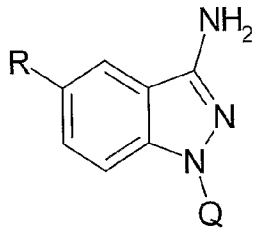
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (X), as set forth in table III, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIb)



(VIb)

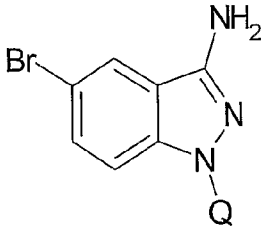
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

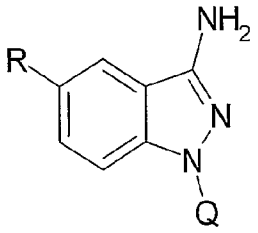
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (XI), as set forth in table IV, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIb)



(VIb)

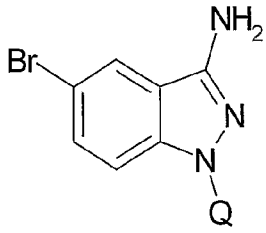
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

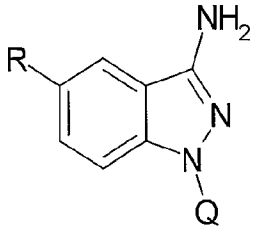
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (XII), as set forth in table V, and by subsequently operating as per step (g) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (VIb)



(VIb)

wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (XIV), as set forth in table VI, in the presence of 4-nitrophenyl-chloroformate, and by subsequently operating as per step (g) of the process.

Table I

Compounds of formula R-B(OH)$_2$ (VII)

1.	2,4-difluorophenylboronic acid
2.	2,4-dimethoxyphenylboronic acid

3.	5-isopropyl-2-methoxybenzeneboronic acid
4.	2,5-difluorophenylboronic acid
5.	2,5-dimethoxyphenylboronic acid
6.	2-methylphenylboronic acid
7.	2-ethoxyphenylboronic acid
8.	(2-methylthio)phenylboronic acid
9.	2,6-dimethylbenzeneboronic acid
10.	(3,4-dimethylphenyl)boronic acid
11.	3,4-dichlorophenylboronic acid
12.	3-chloro-4-fluorobenzeneboronic acid
13.	3-chlorophenylboronic acid
14.	3,5-dimethylphenylboronic acid
15.	3-methylphenylboronic acid
16.	3-acetylphenylboronic acid
17.	3-methoxyphenylboronic acid
18.	2,5-dimethylbenzeneboronic acid
19.	5-fluoro-2-methoxyphenylboronic acid
20.	4-tolylboronic acid
21.	4-acetylphenylboronic acid
22.	(4-isopropylphenyl)boronic acid
23.	4-fluorophenylboronic acid
24.	4-(dimethylamino)phenylboronic acid
25.	4-methoxyphenylboronic acid
26.	4-(trifluoromethoxy)benzeneboronic acid
27.	4-(ethylthiophenyl)boronic acid
28.	3-acetylphenylboronic acid
29.	3-fluorophenylboronic acid
30.	3-acetamidobenzeneboronic acid
31.	3-(trifluoromethoxy)benzeneboronic acid
32.	3-ethoxyphenylboronic acid

33.	phenylboronic acid
34.	2-fluorophenylboronic acid
35.	2-methoxyphenylboronic acid
36.	2-thiopheneboronic acid
37.	thiophene-3-boronic acid
38.	4-cyanophenylboronic acid
40.	(2-cyanophenyl)boronic acid
41.	4-(hydroxymethyl)phenylboronic acid

Table II

Compounds of formula R'CO-Z (IX)

1.	acetyl chloride
2.	isobutyryl chloride
3.	diphenylacetyl chloride
4.	2-phenylbutyryl chloride
5.	dl-2-methylbutyryl chloride
6.	2-ethylhexanoyl chloride
7.	2-n-propyl-n-valeroyl chloride
8.	2-phenoxypropionyl chloride
9.	2,3,6-trifluorobenzoyl chloride
10.	2,4-dimethoxybenzoyl chloride
11.	2-methoxybenzoyl chloride
12.	2-chloro-6-fluorobenzoyl chloride
13.	3,4,5-trimethoxybenzoyl chloride
14.	2,3,4,5-tetrafluorobenzoyl chloride
15.	3,5-dichlorobenzoyl chloride
16.	3-chlorobenzoyl chloride
17.	3-fluorobenzoyl chloride
18.	cyclopropanecarbonyl chloride
19.	2,4-difluorobenzoyl chloride

20.	cyclobutanecarbonyl chloride
21.	cyclopentanecarbonyl chloride
22.	2-furoyl chloride
23.	propionyl chloride
24.	4-methoxyphenylacetyl chloride
25.	3-methoxyphenylacetyl chloride
26.	cyclopentylacetyl chloride
27.	phenylacetyl chloride
28.	butyryl chloride
29.	3-cyclopentylpropionyl chloride
30.	methoxyacetyl chloride
31.	4-chlorophenoxyacetyl chloride
32.	benzyloxyacetyl chloride
33	O-acetylmandelic acid chloride
34	N-(p-toluenesulfonyl)-l-phenylalanyl chloride

Table III

Compounds of formula $R'SO_2$-Z (X)

1.	3,4-dichlorobenzenesulfonyl chloride
2.	2,4-difluorobenzenesulphonyl chloride
3.	3-chloro-2-methylbenzenesulfonyl chloride
4.	4-N-propylbenzenesulfonyl chloride
5.	2-chloro-4-fluorobenzenesulphonyl chloride
6.	3-methoxybenzenesulphonyl chloride
7.	methanesulfonyl chloride
8.	2-thiophenesulfonyl chloride
9.	5-chlorothiophene-2-sulfonyl chloride
10.	5-fluoro-2-methylbenzenesulphonyl chloride

Table IV

Compounds of formula R'-NCO (XI)

1.	isopropyl isocyanate
2.	sec-butyl isocyanate
3.	o-tolyl isocyanate
4.	2-methoxyphenyl isocyanate
5.	3-methoxyphenyl isocyanate
6.	4-methoxyphenyl isocyanate
7.	phenyl isocyanate
8.	ethyl isocyanate
9.	ethyl isocyanatoacetate
10.	n-propyl isocyanate
11.	n-butyl isocyanate

Table V

Compounds of formula R'OCO-Z (XII)

1.	phenyl chloroformate
2.	4-chlorophenyl chloroformate
3.	benzyl chloroformate
4.	isobutyl chloroformate
5.	4-nitrophenyl chloroformate
6.	4-fluorophenyl chloroformate

Table VI

Compounds of formula HNR'R" (XIV)

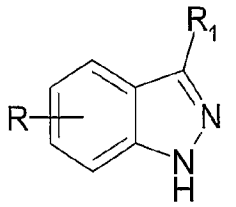
1.	piperidine
2.	butylamine
3.	4-(2-aminoethyl)morpholine
4.	1-(3-aminopropyl)imidazole
5.	piperazine
6.	tetrahydrofurfurylamine
7.	phenethylamine

8.	3-phenylpropylamine
9.	n-propylamine
10.	isobutylamine
11.	cyclopropanemethylamine
12.	2-(2-aminoethyl)-1-methylpyrolidine
13.	4-methylpiperidine
14.	1-methylpiperazine
15.	1-(3-aminopropyl)-2-pyrrolidinone
16.	1,3-diaminopropane
17.	ethylenediamine
18.	4-hydroxypiperidine
19.	3-amino-1-propanol
20.	2-(2-aminoethyl)pyridine
21.	1-(2-aminoethyl)piperidine
22.	pyrrolidine
23.	n-acetylethylenediamine
24.	1-acetylpiperazine
25.	3-methoxypropylamine
26.	3-methylpiperidine
27.	2-methylbutylamine
28.	1-(2-pyridyl)piperazine
29.	4-benzylpiperidine
30.	n,n-diethylnipecotamide
31.	3,5-dimethylpiperidine
32.	2-(aminomethyl)-1-ethylpyrrolidine
33.	1-(2-furoyl)piperazine
34.	thiophene-2-ethylamine
35.	1-(2-aminoethyl)-2-imidazolone
36.	thiomorpholine
37.	propargyl chloroformate

38.	4-piperidinopiperidine
39.	1-piperazinecarboxaldehyde
40.	1-benzylpiperazine
41.	3-piperidinemethanol
42.	3-ethoxypropylamine
43.	isoamylamine
44.	1-(2-fluorophenyl)piperazine
45.	1-(2-hydroxyethyl)-piperazine
46.	n,n-diethylethylenediamine
47.	1-(2-methoxyphenyl)piperazine
48.	4-(1-pyrrolidinyl)piperidine
49.	3-(dimethylamino)propylamine
50.	2-phenyl-propylamine
51.	3-hydroxypiperidine
52.	1-(3 aminopropyl) pyrrolidene
53.	1-hydroxyethylethoxypiperazine
54.	2,6-dimethylpiperazine
55.	3-isopropoxypropylamine
56.	1-(2,3-dimethylphenyl)-piperazine
57.	1-(3-methoxyphenyl)-piperazine
58.	n,n-diisopropylethylenediamine
59.	(r)-(-)-2-methylpiperazine
60.	1-(2,5-dimethylphenyl)piperazine
61.	2-methyl-1-(3-methylphenyl)piperazine
62.	1-cyclohexylpiperazine
63.	2-methylpiperazine
64.	1-(4-fluorophenyl)piperazine
65.	1-ethylpropylamine
66.	dl-alpha-methylbenzylamine
67.	3,4-dimethoxybenzylamine

	[veratrylamine]
68.	2-methylbenzylamine
69.	2-methoxyethylamine
70.	allylamine
71.	azetidine hydrochloride
72.	ammonia

Accordingly, it is a further object of the present invention a library of two or more compounds of formula (I)



(I)

wherein

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heteroatoms selected from S, O and N;

$\mathbf{R_1}$ is an optionally substituted group selected from

-N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

$\mathbf{R_a}$ and $\mathbf{R_b}$ are, each independently, hydrogen or a straight or branched C_1-C_6 alkyl group;

R' and **R"** are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl or aryl C_1-C_6 alkyl wherein aryl is as above defined, or a 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl; or, when taken together with the nitrogen atom to which they are attached, R' and R" may form an optionally substituted 4 to 7 membered heterocycle, optionally containing an additional heteroatom selected from S, O or N.

From all of the above, it is clear to the skilled man that once a library of indazole derivatives is thus prepared, for instance consisting of a few thousands of compounds of formula (I), the said library can be very advantageously used for screening towards given target kinases, as formerly reported.

See, for a general reference to libraries of compounds and uses thereof as tools for screening biological activities, J. Med. Chem. 1999, 42, 2373-2382; and Bioorg. Med. Chem. Lett. 10 (2000), 223-226.

PHARMACOLOGY

The compounds of formula (I) are active as protein kinase inhibitors and are therefore useful, for instance, to restrict the unregulated proliferation of tumor cells.

In therapy, they may be used in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds is determined through a method of assay based on the use of the SPA technology (Amersham Pharmacia Biotech).

The assay consists of the transfer of radioactivity labelled phosphate moiety by the kinase to a biotinylated substrate. The resulting 33P-labelled biotinylated product is allowed to bind to streptavidin-coated SPA beads (biotin capacity 130pmol/mg), and light emitted was measured in a scintillation counter.

Inhibition assay of cdk2/Cyclin A activity

Kinase reaction: 4 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 μM ATP (0.1 microCi $P^{33}\gamma$-ATP), 4.2 ng Cyclin A/CDK2 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 30 min at r.t. incubation, reaction was stopped by 100 μl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μM ATP, containing 1 mg SPA beads. Then a volume of 110 μl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100μl 5M CsCl were added to allow statification of beads to the top of the plate and let stand 4 hours before radioactivity counting in the Top-Count instrument

IC50 determination: inhibitors are tested at different concentrations ranging from 0.0015 to 10 μM. Experimental data are analyzed by the computer program GraphPad Prizm using the four parameter logistic equation:

y = bottom+(top-bottom)/(1+10^((logIC50-x)*slope))

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

Ki calculation:

Experimental method: Reaction was carried out in buffer (10 mM Tris, pH 7.5, 10 mM $MgCl_2$, 0.2 mg/ml BSA, 7.5 mM DTT) containing 3.7 nM enzyme, histone and ATP (constant ratio of cold/labeled ATP 1/3000). Reaction was stopped with EDTA and the substrate captured on phosphomembrane (Multiscreen 96 well plates from Millipore). After extensive washing, the multiscreen plates are read on a top counter. Control (time zero) for each ATP and histone concentrations was measured.

Experimental design: Reaction velocities are measured at different four ATP, substrate (histone) and inhibitor concentrations. An 80-point concentration matrix was designed around the respective ATP and substrate Km values, and the inhibitor IC50 values (0.3, 1, 3, 9 fold the Km or IC50 values). A preliminary time course experiment in the absence of inhibitor and at the different ATP and substrate concentrations allow the selection of a single endpoint time (10 min) in the linear range of the reaction for the Ki determination experiment.

Kinetic parameter estimates: Kinetic parameters were estimated by simultaneous nonlinear least-square regression using [Eq.1] (competitive inhibitor respect to ATP, random mechanism) using the complete data set (80 points):

$$v = \frac{Vm \bullet A \bullet B}{\alpha \bullet Ka \bullet Kb + \alpha \bullet Ka \bullet B + \alpha \bullet Kb \bullet A + A \bullet B + \alpha \bullet \frac{Ka}{Ki} \bullet I \bullet (Kb + \frac{B}{\beta})} \qquad \text{[Eq.1]}$$

where A=[ATP], B=[Substrate], I=[inhibitor], Vm= maximum velocity, Ka, Kb, Ki the dissociation constants of ATP, substrate and inhibitor respectively. α and β the cooperativity factor between substrate and ATP binding and substrate and inhibitor binding respectively.

In addition the selected compounds have been characterized on a panel of ser/threo kinases strictly related to cell cycle (cdk2/cyclin E, cdk1/cyclin B1, cdk5/p25, cdk4/ cyclin D1), and also for specificity on MAPK, PKA, EGFR, IGF1-R, and Aurora-2.

Inhibition assay of cdk2/Cyclin E activity

Kinase reaction: 10 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 30 μM ATP (0.3 microCi $P^{33}\gamma$-ATP), 4 ng GST-Cyclin E/CDK2 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 60 min at r.t. incubation, reaction was stopped by 100 μl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μM ATP, containing 1 mg SPA beads. Then a volume of 110 μl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100μl 5M CsCl were added to allow statification of beads to the top of the plate and let stand 4 hours before radioactivity counting in the Top-Count instrument

IC50 determination: see above

Inhibition assay of cdk1/Cyclin B1 activity

Kinase reaction: 4 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 20 μM ATP (0.2 microCi $P^{33}\gamma$-ATP), 3 ng Cyclin B/CDK1 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 20 min at r.t. incubation, reaction was stopped by 100 μl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μM ATP, containing 1 mg SPA beads. Then a volume of 110 μl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100μl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of cdk5/p25 activity

The inhibition assay of cdk5/p25 activity was performed according to the following protocol.

Kinase reaction: 10 μM biotinylated histone H1 (Sigma # H-5505) substrate, 30 μM ATP (0.3 microCi $P^{33}\gamma$-ATP), 15 ng CDK5/p25 complex, inhibitor in a final volume of

30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 30 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100µl 5M CsCl were added to allow statification of beads to the top of the plate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of cdk4/Cyclin D1 activity

Kinase reaction: 0,4 uM µM mouse GST-Rb (769-921) (# sc-4112 from Santa Cruz) substrate, 10 µM ATP (0.5 µCi $P^{33}\gamma$-ATP), 100 ng of baculovirus expressed GST-cdk4/GST-Cyclin D1, suitable concentrations of inhibitor in a final volume of 50 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 40 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 60 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled Rb fragment was detected by radioactivity counting in the Top-Count instrument.

IC50 determination: see above.

Inhibition assay of MAPK activity

Kinase reaction: 10 µM in house biotinylated MBP (Sigma # M-1891) substrate, 15 µM ATP (0.15 microCi $P^{33}\gamma$-ATP), 30 ng GST-MAPK (Upstate Biothecnology # 14-173), inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 30 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above.

Inhibition assay of PKA activity

Kinase reaction: 10 µM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 µM ATP (0.2 microM $P^{33}\gamma$-ATP), 0.45 U PKA (Sigma # 2645), inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 90 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above.

Inhibition assay of EGFR activity

Kinase reaction: 10 µM in house biotinylated MBP (Sigma # M-1891) substrate, 2 µM ATP (0.04 microCi $P^{33}\gamma$-ATP), 36 ng insect cell expressed GST-EGFR, inhibitor in a final volume of 30 µl buffer (Hepes 50 mM pH 7.5, $MgCl_2$ 3 mM, $MnCl_2$ 3 mM, DTT 1 mM, $NaVO_3$ 3µM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 20 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above.

Inhibition assay of IGF1-R activity

The inhibition assay of IGF1-R activity is performed according to the following protocol.

Kinase reaction: 10 µM biotinylated MBP (Sigma cat. # M-1891) substrate, 0-20 µM inhibitor, 6 µM ATP, 1 microCi ^{33}P-ATP, and 22.5 ng GST-IGF1-R (pre-incubated for

30 min at room temperature with cold 60 μM cold ATP) in a final volume of 30 μl buffer (50 mM HEPES pH 7.9, 3 mM $MnCl_2$, 1 mM DTT, 3 μM $NaVO_3$) were added to each well of a 96 U bottom well plate. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 μl PBS buffer containing 32 mM EDTA, 500 μM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

Inhibition assay of Aurora-2 activity

Kinase reaction: 8 μM biotinylated peptide (4 repeats of LRRWSLG), 10 μM ATP (0.5 uCi P^{33}g-ATP), 15 ng Aurora2, inhibitor in a final volume of 30 μl buffer (HEPES 50 mM pH 7.0, $MgCl_2$ 10 mM, 1 mM DTT, 0.2 mg/ml BSA, 3□M orthovanadate) were added to each well of a 96 U bottom well plate. After 30 minutes at room temperature incubation, reaction was stopped and biotinylated peptide captured by adding 100 μl of bead suspension.

Stratification: 100 μl of CsCl2 5 M were added to each well and let stand 4 hour before radioactivity was counted in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of Cdc7/dbf4 activity

The inhibition assay of Cdc7/dbf4 activity is performed according to the following protocol.

The Biotin-MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with γ^{33}-ATP. The phosphorylated Biotin-MCM2 substrate is then captured by Streptavidin-coated SPA beads and the extent of phosphorylation evaluated by β counting.

The inhibition assay of Cdc7/dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added :

- 10 μl substrate (biotinylated MCM2, 6 μM final concentration)
- 10 μl enzyme (Cdc7/Dbf4, 12.5 nM final concentration)

- 10 µl test compound (12 increasing concentrations in the nM to µM range to generate a dose-response curve)
- 10 µl of a mixture of cold ATP (10µM final concentration) and radioactive ATP (1/2500 molar ratio with cold ATP) was then used to start the reaction which was allowed to take place at 37°C.

Substrate, enzyme and ATP were diluted in 50 mM HEPES pH 7.9 containing 15 mM $MgCl_2$, 2 mM DTT, 3 µM $NaVO_3$, 2mM glycerophosphate and 0.2mg/ml BSA. The solvent for test compounds also contained 10% DMSO.

After incubation for 20 minutes, the reaction was stopped by adding to each well 100 µl of PBS pH 7.4 containing 50 mM EDTA, 1 mM cold ATP, 0.1% Triton X100 and 10 mg/ml streptavidin coated SPA beads.

After 15 minutes of incubation at room temperature to allow the biotinylated MCM2-streptavidin SPA beads interaction to occur, beads were trapped in a 96 wells filter plate (Unifilter^{R} GF/B^{TM}) using a Packard Cell Harvester (Filtermate), washed with distilled water and then counted using a Top Count (Packard).

Counts were blank-subtracted and then the experimental data (each point in triplicate) were analyzed for IC50 determination using a non-linear regression analysis (Sigma Plot).

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and the administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

In addition, the compounds of the invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents,

immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), metallomatrixprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents, farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic , magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulfates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerin and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty ester surfactant or lecithin.

The following examples are herewith intended to better illustrate the present invention without posing any limitation to it.

General Methods

Flash Chromatography was performed on silica gel (Merck grade 9395, 60A).

The samples were analyzed by using the following two methods:

Method I: the analysis was performed on Waters X Terra 18 (4,6 x 50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid/acetonitrile 95:5), and Mobile phase B was H_2O/acetonitrile (5:95). Gradient from 10 to 90% B in 8 minutes, hold 90% B 2 minutes. UV detection at 220 nm and 254 nm. Flow rate 1 ml /min. Injection volume 10 μl. Full scan, mass range from 100 to 800 amu. Capillary voltage was 2.5 KV; source temp. was 120°C; cone was 10 V. Retention times (HPLC r.t.) are given in minutes at 220 nm or at 254 nm. Mass are given as m/z ratio.

Method II: the analysis was performed on LCMS instrument comprising: Hewlett Packard 1312A binary pump; Gilson 215 autosampler fitted with a 1ml syringe; Polymer

Labs PL1000 Evaporative Light Scattering Detector; Micromass ZMD mass spectrometer operating in Electrospray positive ionisation mode.

The LC eluent is split and approximately 200 µl/min enters the mass spectrometer, 800 µl/min to the ELS. The instruments are currently controlled using Micromass MassLynx 3.5 software under Windows NT4.0

HPLC Conditions:

Mobile Phase: Aqueous - Water + 0.1% Trifluoroacetic acid

Organic - Acetonitrile + 0.1% Trifluoroacetic acid

Gradient:	Time (mins)	% Aqueous	% Organic
	0.0	100	0
	1.8	5	95
	2.1	5	95
	2.3	100	0
	2.4	100	0

Run time: 2.4 mins

Flow rate: 1 ml/min

Injection vol: 3 µl

Column temperature: ambient (20°C)

Column: 50 x 2.0mm Hypersil C18 BDS; 5µm

ELS Detector Nebuliser Temperature 80°C

Evaporation temperature 90°C

Gas Flow 1.5 l/hr

MS Detector: m/z 150-800 at 0.5 secs/scan, 0.1 second interscan delay;

Cone voltage 25V, Source Temp. 140°C

Drying Gas 350 l/hr

When necessary, compounds have been purified by preparative HPLC; two different instruments were used:

Instrument 1: Waters Symmetry C18 (19 x 50 mm, 5 µm) Column, HPLC 600

instrument equipped with a 996 Waters PDA detector and a Micromass mod. ZMD single quadrupole mass spectrometer, electron spray ionization, positive mode. Mobile phase A was water 0.1% formic acid, and Mobile phase B was acetonitrile. Gradient from 10 to 90% B in 8 min, hold 90% B 2 min. Flow rate 20 ml/min.

Instrument 2: Waters Symmetry C18 (4.6 x 50 mm, 3.5 μm) Column; HPLC 600 instrument equipped with a 996 Waters PDA detector and a Micromass mod. ZMD single quadrupole mass spectrometer, electron spray ionization, positive mode. Mobile phase A was 95% aq. NH_4OAc (5 mM) pH 5/ 5% MeCN, and Mobile phase B was 5% H_2O / 95% MeCN. Gradient from 10 to 90% B in 8 min, hold 90% B 2 min. Flow rate 1 ml/min.

1H-NMR spectrometry was performed on a Mercury VX 400 operating at 400.45 MHz equipped with a 5 mm double resonance probe [1H (15N-31P) ID-PFG Varian].

As formerly indicated, several compounds of formula (I) of the invention have been synthesized in parallel, according to combinatorial chemistry techniques.

In this respect, some compounds thus prepared have been conveniently and unambiguously identified, as per the coding system of tables X and XI, together with HPLC retention time and experimentally found [M+H]+.

Each code, which unambiguosly identifies a single specific compound of formula (I) only, consists of three units A-M-B or, alternatively, A-M-C.

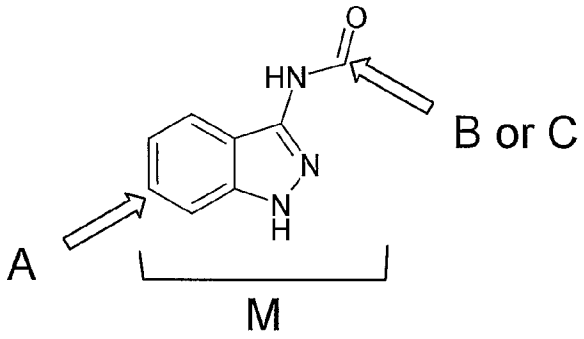
Code A represents any R substituent, as per formula (I), being attached to the rest of the indazole moiety in position 6; each A group is represented through the proper chemical formula in the following table VII, together with its point of attachment to the rest of the molecule M.

Code M refers to the central core of the indazole moiety which bears, in position 3, an amido group (-NHCO-) and is further substituted in position 6 by the aforementioned A group.

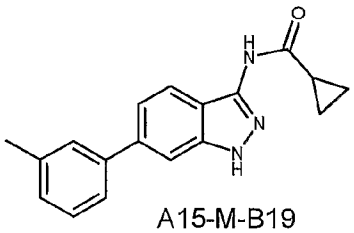
Codes B and C represent the groups which are linked to the above amido portion so as to give rise to -NHCO-B or -NHCO-C groups R_1, as per formula (I).

Each B and C group is represented through the proper chemical formula in the following tables VIII and IX, respectively; the point of attachment of B and C groups to the rest of the molecule M is also clearly indicated in tables VIII and IX.

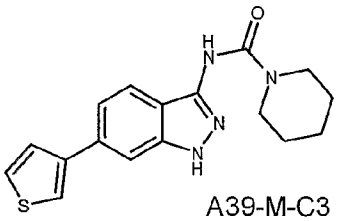
Therefore, the coding system presently used for some of the compounds of formula (I) can be shortly summarised as follows:



Just as an example, which is not intended to limit the scope of the present invention, the compound A15-M-B19 of table X (see example 6, entry 1) represents the 3-amido indazole moiety M being substituted in position 6 by the group A15 and at the amido portion by the group B19; likewise, the compound A39-M-C3 of table XI (see example 8, entry 26) represents a 3-amido-indazole moiety M being substituted in position 6 by the group A39 and at the amido portion by the group C3.



A15-M-B19



A39-M-C3

Table VII A groups

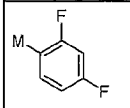
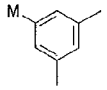
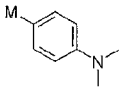
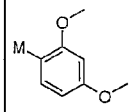
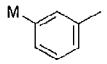
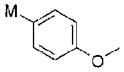
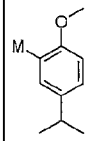
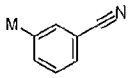
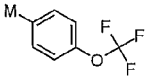
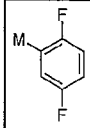
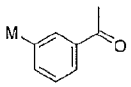
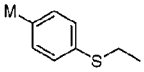
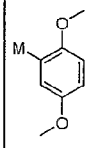
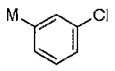
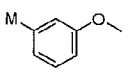
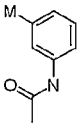
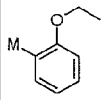
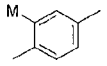
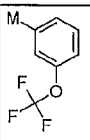
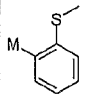
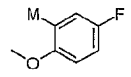
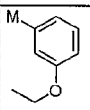
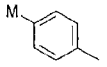
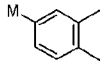
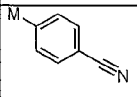
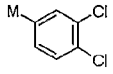
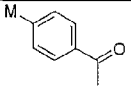
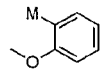
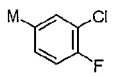
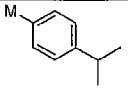
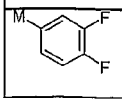
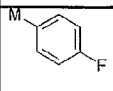
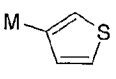
Fragment	Code	Fragment	Code	Fragment	Code
	A1		A14		A27
	A2		A15		A28
	A3		A16		A29
	A4		A17		A30
	A5		A18		A31
	A6		A19		A32
	A7		A20		A33
	A8		A21		A34
	A9		A22		A35
	A10		A23		A36
	A11		A24		A37
	A12		A25		A38
	A13		A26		A39

Table VIII - B groups

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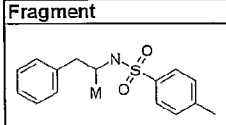
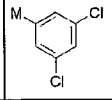
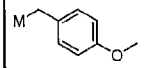
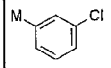
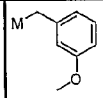
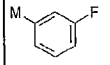
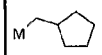
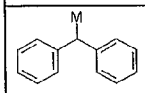
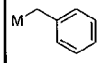
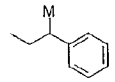
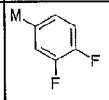
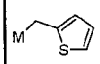
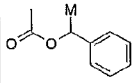
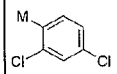
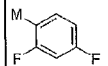
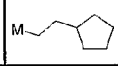
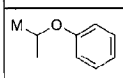
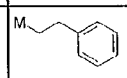
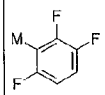
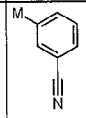
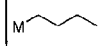
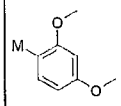
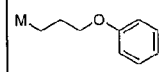
	B1		B16		B31
	B2		B17		B32
	B3		B18		B33
	B4		B19		B34
	B5		B20		B35
	B6		B21		B36
	B7		B22		B37
	B8		B23		B38
	B9		B24		B39
	B10		B25		B40
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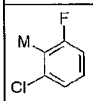
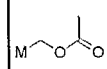
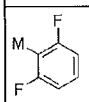
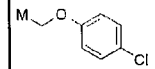
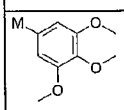
	B12		B27		B42
	B13		B28		B43
	B14		B29		B44
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Table IX- C Groups

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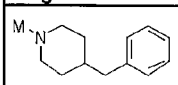
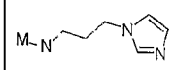
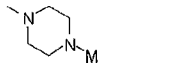
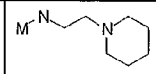
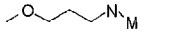
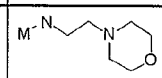
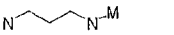
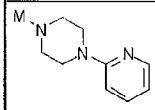
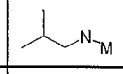
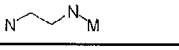
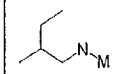
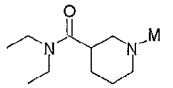
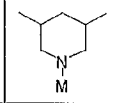
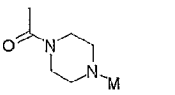
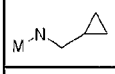
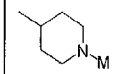
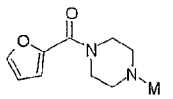
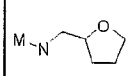
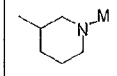
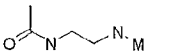
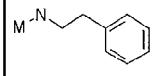
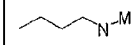
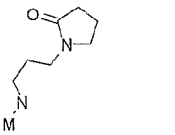
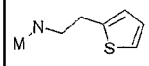
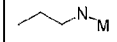
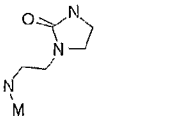
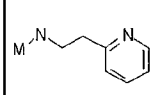
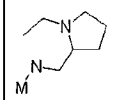
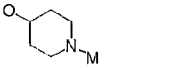
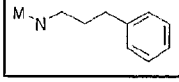
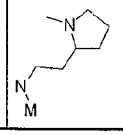
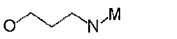
	C1		C13		C25
	C2		C14		C26
	C3		C15		C27
	C4		C16		C28
	C5		C17		C29
	C6		C18		C30
	C7		C19		C31
	C8		C20		C32
	C9		C21		C33
	C10		C22		C34
	C11		C23		C35
	C12		C24		C36

Example 1

6-bromo-1H-indazol-3-amine

4-bromo-2-fluorobenzonitrile (67.8 g), hydrazine hydrate (32.8 ml) in n-butanol (410 ml) were heated to 112°C for five hours. The reaction mixture was allowed to cool down to r.t. The precipitated crystalline solid was filtered off and washed three times with ethylacetate (100 ml each). The product was dried in vacuo at 40°C. mp. 222-225°C $[M+H]^+$= 213; ^{1}H-NMR (300MHz DMSO-d_6): 11.43 (s, 1H); 7.61 (d, 1H): 7.4 (d, 1H); 7.0 (d of d, 1H); 5.4 (s, 2H)

Example 2

N'-(6-bromo-1H-indazol-3-yl)-N,N-dimethylimidoformamide

6-bromo-1H-indazol-3-amine (70.5 g) was suspended in dimethylformamide dimethylacetal (600 ml). After one hour the solid was completely into solution. After 1.5 hours a white crystalline solid appeared and after 5 hours HPLC indicated complete conversion. The reaction mixture was evaporated in vacuo to give an oil, which was precipitated into MeCN/H_2O 1/1 (v/v). The crystalline, yellowish solid was stirred for another 15 min., then filtered and washed subsequently with H_2O (100 ml). The solid was then washed with DCM (2x250 ml). The DCM-filtrates contained some product which could be retrieved upon crystallization at –10°C.

tlc: Rf: 0.24 (DCM, EtOAc, MeCN)60/35/5 (v/v/v); $[M+H]^+$=269; ^{1}H-NMR (300MHz DMSO-d_6): 12.3 (s, 1H); 8.19 (s, 1H); 7,5-7.6 (s, d, 2H); 7.08 (d of d, 1H) 3.02, 2.98 (two s, 6H)

^{1}H-NMR of the TFA-salt of N'-(6-bromo-1H-indazol-3-yl)-N,N-dimethylimidoformamide

(300MHz DMSO-d_6): 8.79 (s, 1H); 7.89 (d of d, J=8.8, J'=0.5 1H); 7.79 (m, 1H); 7.35 (d of d, J=8.8, J'=1.7 1H) 3.40(s, 3H); 3.29(s, 3H).

Example 3

N'-(6-bromo-1-trityl resin-1H-indazol-3-yl)-N,N-dimethylimidoformamide

To commercial polystyrene resin bearing TritylChloride (loading 0.75-1.35 mmol/g, 125 g) and 6-bromo-1H-indazol-3-amine (62.5 g), 62.5 ml of dry 1,8-diazabiciclo[5.4.0]undec-7-ene (DBU) and dry dimethylformamide (900 ml) were added. The slurry was stirred for 48 hours at room temperature under exclusion of moisture with a mechanical overhead stirrer. An aliquot of the slurry containing 10-50 mg of resin

was removed from the reaction mixture, transferred into a sinter glass frit with a valve on its bottom and washed the following way:

3x a) 1 ml DMF; b) 1 ml H_2O

2x a) 1 ml MeOH; b) 1 ml DMF

1x1 ml MeOH

2x a) 1 ml toluene; 1 ml diethylether

3x1 ml diethylether.

The resin was dried in vacuo, then weighed.

From the known amount of resin the bound indazole was determined upon cleavage using TFA whereby collecting the cleavage solutions. The cleavage was performed the following way:

1x0.5 ml 20% TFA/DCM 5 min.

4x0.2 ml 20% TFA/DCM 2 min.

The combined cleavage solutions combined and then dried in vacuo. The dried TFA-salt of the N'-(6-bromo-1H-indazol-3-yl)-N,N-dimethylimidoformamide was weighed, and analyzed. The weight of the recovered material revealed the loading of the resin. When the loading exceeded 0.7 mmol/g the immobilization reaction was quenched upon addition of MeOH (100 ml).

The slurry was transferred into a commercial "resin wash station" (Rink) an washed as follows:

3x700 ml DMF: the effluent from the washing vessel was collected to recover unused indazole.

3x a) 700 ml DMF; b) 700 ml H_2O

2x a) 700 ml MeOH; b) 700 ml DMF

1x700 ml MeOH

2x a) 700 ml toluene; 700 ml diisopropylether

3x 700 ml diisopropylether.

The resin was dried in vacuo until constancy of weight. The weight of the resin revealed the loading of the indazole. The loading determined by weight increase corresponded to that determined by cleavage.

Example 4

6-bromo-1-trityl resin-1H-indazol-3-amine

Trityl-resin bearing N'-(6-bromo-1H-indazol-3-yl)-N,N-dimethylimidoformamide (23.44 g) with a loading of 0.74 mmol/g was stirred in a 0.2 M solution of hydrazine hydrate (H_2N-NH_2·H_2O)in pyridine/acetic acid 4/1(V/V)(250 ml) for 48 hours at 80°C using a mechanical overhead stirrer. An aliquot of the slurry containing 10-50 mg of resin was removed from the reaction mixture, transferred into a sinter glass frit with a valve on its bottom and washed the following way:

3x a) 1 ml DMF; b) 1 ml H_2O

2x a) 1 ml MeOH; b) 1 ml DMF

1x1 ml MeOH

2x a) 1 ml toluene; 1 ml diethylether

3x1 ml diethylether.

The resin was dried in vacuo, then weighed.

From the known amount of resin the bound indazole was determined upon cleavage using TFA whereby collecting the cleavage solutions. The cleavage was performed the following way:

1x 0.5 ml 20% TFA/DCM 5 min.

4x 0.2 ml 20% TFA/DCM 2 min.

The combined cleavage solutions were combined and then dried in vacuo. The dried TFA-salt of the 6-bromo-3-amino indazole was weighed, and analyzed. The HPLC-trace at 215 nm indicated complete removal of the amidine protective group. If remaining starting material was still present, the amidine removal was allowed to continue for another day.

The bulk resin work up was performed as follows:

The slurry was transferred into a commercial "resin wash station" (Rink) an washed as follows:

3x 700 ml DMF: The effluent from the washing vessel is collected to recover unused indazole.

3x a) 700 ml DMF; b) 700 ml H_2O

2x a) 700 ml MeOH; b) 700 ml DMF

1x 700 ml MeOH

2x a) 700 ml toluene; 700 ml diisopropylether

3x 700 ml diisopropylether.

The resin was dried in vacuo until constancy of weight.

Example 5

6-(4-methoxyphenyl)-1H-indazol-3-amine

A commercial "Miniblock" reactor was charged with trityl-resin bearing 6-bromo-1H-indazol-3-amine (95 mg, 0.066 mmol); 4-methoxyphenylboronic acid (0.3 mmol); Pd_2dba_3 (5 mg). Subsequently the reactor was sealed and the reaction mixture was put under inert atmosphere (N_2 or Ar).

The following solutions were prepared:

Triphenylphosphine in DME:

Triphenylphosphine (7.7 mmol, 2.02 g) was dissolved in DME (HPLC-grade) 275 ml. The pressure of the air in the headspace of the flask containing the solution was reduced to 20 mBar for 5 min., while being sonicated. Then headspace was filled with argon or nitrogen until ambient pressure was achieved. This process was repeated two more time to afford the solution sufficiently freed of oxygen.

10% aq. K_3PO_4:

The solution was prepared from K_3PO_4 and distilled or diionized water. The obtained solution was degassed and saturated with nitrogen or argon like the tripenylphosphine solution.

To the solids in the sealed reactor being under inert atmosphere was added degassed triphenylphosphine solution in DME (2 ml) and aq. K_3PO_4 solution (0.5 ml). The sealed reactor was shaken and heated to 80°C for 48 hours.

The reaction solvent was drained and the resin was washed the following way:

3x a) 1 ml DMF; b) 1 ml H_2O

3x a) 1 ml MeOH; b) 1 ml DMF

3x a) 1 ml MeOH; b) 1 ml DCM

3x a) 1 ml DCM; b) diethyl ether

3x diethyl ether.

The resin may either be subjected to acylation reactions or the product may be cleaved directly.

The cleavage was performed the following way:

1x 0.5 ml 20% TFA/DCM 5 min.

4x 0.2 ml 20% TFA/DCM 2 min.

The combined cleavage solutions were combined and then dried. The solid, which may contain residual Pd was taken up in DMSO and filtered to remove particular matter such as Pd-metal. The cleared DMSO solution was subjected to preparative reverse phase HPLC (C-18) using a gradient of water, 0.1% formic acid and MeCN 10-90% vol. within 8 min.

The product fractions were collected and those containing product pooled. Evaporation of the solvent then gave the dried 6-(4-methoxyphenyl)-1H-indazol-3-amine as a dried powder.

$[M+H]^+ = 240.09$; ^{1}H-NMR (300MHz DMSO-d_6): 11.33 (s, 1H); 7.7 (d, J=8, 1H); 7.61 (d, J=9, 2H); 7.33 (m, 1H); 7.14 (d of d J=8, J'=1, 1H); 7.01 (d, J=9, 2H); 5.3 (s, 2H); 3.79 (s, 3H)

By working in an analogous way the following products were cleaved from the resin:

6-(4-fluorophenyl)-1H-indazol-3-amine

$[M+H]^+ = 228.07$; ^{1}H-NMR (300MHz DMSO-d_6): 11.41 (s, 1H); 7.74-7.68 (m, 3H); 7.37 (d, J=7.5, 1H); 7.26 (t, J=9, 2H); 7.16 (d, J=8, 1H); 5.33 (s, 2H).

6-thien-3-yl-1H-indazol-3-amine

$[M+H]^+ = 216.08$; ^{1}H-NMR (300MHz DMSO-d_6): 11.36 (s, 1H); 7.85 (m, 1H); 7.66 (d, J=8, 1H); 7.63-7.60 (m, 1H); 7.57-7.55 (m, 1H); 7.46 (m, 1H); 7.25 (d of d, J=8, J'=1, 1H); 5.3 (s, 2H)

6-(1-naphthyl)-1H-indazol-3-amine $[M+H]^+ = 260.15$; ^{1}H-NMR (300MHz DMSO-d_6): 11.42 (s, 1H); 8.02-7.92 (4m, 2H); 7.86-7.77(4s, 2H); 7.6-7.42 (m, 4H); 7.23 (m, 1H); 9.95-7 (d, J=9, 1H)

6-(2,6-dimethylphenyl)-1H-indazol-3-amine HPLC r.t. (Method I): 5.29; $[M+H]^+ = 238.19$

6-(1,3-benzodioxol-5-yl)-1H-indazol-3-amine HPLC r.t. (Method I): 4.47; $[M+H]^+ = 254.1$

6-(1-benzofuran-2-yl)-1H-indazol-3-amine HPLC r.t. (Method I): 5.43; $[M+H]^+$ = 250.7

6-(2,5-dimethylphenyl)-1H-indazol-3-amine HPLC r.t. (Method I): 5.42; $[M+H]^+$ = 238.2

1-[4-(3-amino-1H-indazol-6-yl)phenyl]ethanone HPLC r.t. (Method I): 4.06; $[M+H]^+$ = 252.1

6-(2-fluorophenyl)-1H-indazol-3-amine HPLC r.t. (Method I): 4.65; $[M+H]^+$= 228.11

6-[4-(dimethylamino)phenyl]-1H-indazol-3-amine HPLC r.t. (Method II): 0.85 [M+H]+ = 253.1

6-(2,5-dimethoxyphenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.12 [M+H]+ = 270.1

6-(3-methylphenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.15 [M+H]+ = 224.1

6-(3-chlorophenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.17 [M+H]+ = 244.1

6-(3-fluorophenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.1 [M+H]+ = 228.1

6-(2,4-dimethoxyphenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.09 [M+H]+ = 270.1

6-(2,5-difluorophenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.1 [M+H]+ = 246.1

3-(3-amino-1H-indazol-6-yl)benzonitrile HPLC r.t. (Method II): 1.02 [M+H]+ = 235.1

6-(2,5-dimethylphenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.2 [M+H]+ = 238.1

6-(5-fluoro-2-methoxyphenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.1 [M+H]+ = 258.1

6-(2-methoxyphenyl)-1H-indazol-3-amine HPLC r.t. (Method II): 1.08 [M+H]+ = 240.1

Example 6

N-(6-bromo-1H-indazol-3-yl)-2,2-dimethylpropanamide

The reaction was performed in a "Miniblock" reactor (Bohdan) charged with Trityl-resin bearing 6-bromo-1H-indazol-3-amine. To resin (23.5 mg) bearing 6-bromo-1H-indazol-3-amine (1.2 mmol/g) was added N-methylimidazole (0.5 ml) distilled over sodium hydride, and a solution of pivaloyl chloride (0.5 mmol) in DCM (2 ml). The reaction mixture was shaken for 4 hours at room temperature.

The resin was washed as follows:

5x a) 1 ml DMF; b) 1 ml H_2O

The resulting imids of 6-bromo-1H-indazol-3-amine could be either isolated or converted to amides using an appropriate base such as aqueous ammonia. The ammonia treatment could be performed prior or post cleavage from the resin:

Aqueous ammonium hydroxide (20%) was dissolved in ice cold dioxane to afford a solution ammonia/dioxane 1:4 V/V. This solution was added to the appropriate reactor, which was then sealed and agitated at 55°C for 48 hours. The resins were then washed

5x a) 1 ml DMF; b) 1 ml H_2O

5x a) 1 ml MeOH; b) 1 ml DCM

5x a) 1 ml DCM

The cleavage was performed the following way:

1x 0.5 ml 20% TFA/DCM 5 min.

4x 0.2 ml 20% TFA/DCM 2 min.

The combined cleavage solutions were combined and then dried.

The solid, was taken up in DMSO and filtered to remove particular matter. The cleared DMSO solution was subjected to preparative reverse phase HPLC (C-18) using the instrument 1 (see above).

The product fractions were collected and those containing product pooled. Evaporation of the solvent then gave the dried N-(6-bromo-1H-indazol-3-yl)-2,2-dimethylpropanamide as a dried powder.

HPLC r.t. (Method I): 5.21; MS: $[M+H]^+ = 298.08$; $[M-H]^- = 296.08$.

By working in an analogous way, starting from 6-bromo-1H-indazol-3-amine or 6-aryl-1H-indazol-3-amine derivatives (the latter being obtained according the procedure for 6-(4-methoxyphenyl)-1H-indazol-3-amine, the following products were cleaved from the resin:

N-(6-bromo-1H-indazol-3-yl)-2-phenylacetamide

HPLC r.t. (Method I): 5.66; $[M+H]^+ = 332.04$.

N-(6-bromo-1H-indazol-3-yl)benzamide

HPLC r.t. (Method I): 5.65; $[M+H]^+ = 317.99$; $[M-H]^- = 316.04$.

N-(6-bromo-1H-indazol-3-yl)-2-methylbenzamide

HPLC r.t. (Method I): 5.85; $[M+H]^+ = 332.01$; $[M-H]^- = 330$.

N-(6-bromo-1H-indazol-3-yl)-2-methoxybenzamide

HPLC r.t. (Method I): 6.13; $[M+H]^+ = 348.03$.

N-(6-bromo-1H-indazol-3-yl)-2-(trifluoromethyl)benzamide HPLC r.t. (Method I): 6.10; $[M+H]^+ = 386.01$; $[M-H]^- = 384$.

N-(6-bromo-1H-indazol-3-yl)propanamide

HPLC r.t. (Method I) 4.17; $[M+H]^+ = 270$; $[M-H]^- = 268$.

By proceeding in the same way (example 6), 872 products were synthesized in parallel and coded in table X, as formerly indicated; related HPLC retention time (Method II) and the experimentally found [M+H]+ are reported.

Table X

Entry	Compound	r.t. (min)	[M+H]+
1	A15-M-B19	1.38	292.1
2	A15-M-B3	1.4	294.2
3	A15-M-B8	1.58	372.2
4	A15-M-B25	1.51	320.2
5	A15-M-B23	1.44	306.2
6	A32-M-B37	1.36	391.2
7	A32-M-B36	1.1	337.2
8	A32-M-B8	1.3	415.2
9	A24-M-B37	1.49	376.2
10	A24-M-B31	1.51	400.2
11	A24-M-B36	1.23	322.2
12	A24-M-B19	1.2	320.1
13	A24-M-B3	1.22	322.2
14	A24-M-B8	1.42	400.2
15	A24-M-B25	1.34	348.2

Entry	Compound	r.t. (min)	[M+H]+
16	A24-M-B23	1.27	334.2
17	A12-M-B36	1.45	332.1
18	A12-M-B19	1.42	330.1
19	A12-M-B3	1.44	332.1
20	A12-M-B8	1.61	410.1
21	A12-M-B41	1.35	334.1
22	A18-M-B36	1.43	314.1
23	A18-M-B19	1.41	312.1
24	A18-M-B3	1.43	314.1
25	A18-M-B8	1.6	392.1
26	A18-M-B41	1.34	316.1
27	A18-M-B23	1.47	326.1
28	A11-M-B3	1.53	348.1
29	A11-M-B8	1.69	426.1
30	A11-M-B41	1.43	350

Entry	Compound	r.t. (min)	[M+H]+
31	A31-M-B37	1.61	352.2
32	A31-M-B19	1.33	296.1
33	A31-M-B3	1.35	298.1
34	A31-M-B8	1.52	376.1
35	A31-M-B25	1.46	324.1
36	A31-M-B41	1.26	300.1
37	A31-M-B23	1.39	310.1
38	A29-M-B37	1.73	418.2
39	A29-M-B36	1.5	364.1
40	A29-M-B19	1.48	362.1
41	A29-M-B3	1.5	364.1
42	A29-M-B8	1.66	442.1
43	A29-M-B25	1.6	390.1
44	A29-M-B23	1.53	376.1
45	A15-M-B32	1.5	372.2
46	A15-M-B4	1.69	418.2
47	A15-M-B44	1.56	372.2
48	A15-M-B29	1.41	318.1
49	A15-M-B33	1.57	334.2
50	A15-M-B11	1.58	358.2
51	A15-M-B18	1.55	346.1
52	A15-M-B17	1.63	362.1
53	A15-M-B14	1.5	418.2
54	A15-M-B16	1.77	396.1

Entry	Compound	r.t. (min)	[M+H]+
55	A15-M-B10	1.59	388.2
56	A15-M-B9	1.55	382.1
57	A32-M-B32	1.22	415.2
58	A32-M-B4	1.43	461.2
59	A32-M-B14	1.21	461.2
60	A24-M-B4	1.55	446.2
61	A24-M-B44	1.4	400.2
62	A24-M-B29	1.23	346.1
63	A24-M-B33	1.4	362.2
64	A24-M-B18	1.39	374.1
65	A24-M-B17	1.46	390.1
66	A24-M-B14	1.34	446.2
67	A24-M-B10	1.43	416.2
68	A24-M-B9	1.38	410.1
69	A12-M-B44	1.6	410.1
70	A12-M-B11	1.63	396.1
71	A12-M-B14	1.54	456.1
72	A12-M-B9	1.59	420
73	A18-M-B44	1.59	392.1
74	A18-M-B29	1.43	338.1
75	A18-M-B11	1.62	378.1
76	A18-M-B18	1.58	366.1
77	A18-M-B14	1.53	438.1
78	A18-M-B16	1.79	416

Entry	Compound	r.t. (min)	[M+H]+
79	A18-M-B10	1.62	408.1
80	A18-M-B9	1.58	402.1
81	A11-M-B44	1.67	426.1
82	A11-M-B18	1.68	400
83	A11-M-B14	1.62	472.1
84	A31-M-B4	1.65	422.2
85	A31-M-B44	1.51	376.1
86	A31-M-B33	1.52	338.2
87	A31-M-B11	1.54	362.1
88	A31-M-B14	1.45	422.1
89	A31-M-B16	1.72	400
90	A31-M-B10	1.54	392.1
91	A31-M-B9	1.51	386.1
92	A29-M-B44	1.64	442.1
93	A29-M-B29	1.5	388.1
94	A29-M-B11	1.67	428.1
95	A29-M-B14	1.58	488.1
96	A29-M-B9	1.63	452.1
97	A15-M-B15	1.62	400.1
98	A15-M-B43	1.59	392.1
99	A15-M-B27	1.53	334.2
100	A15-M-B1	1.59	525.2
101	A15-M-B22	1.53	364.1
102	A32-M-B43	1.32	435.1

Entry	Compound	r.t. (min)	[M+H]+
103	A32-M-B1	1.34	568.2
104	A24-M-B27	1.37	362.2
105	A24-M-B22	1.36	392.1
106	A12-M-B15	1.65	438
107	A12-M-B43	1.62	430
108	A12-M-B22	1.57	402.1
109	A18-M-B15	1.64	420
110	A18-M-B12	1.54	400
111	A18-M-B43	1.62	412.1
112	A18-M-B22	1.56	384.1
113	A11-M-B15	1.74	454
114	A31-M-B43	1.55	396.1
115	A31-M-B22	1.49	368.1
116	A29-M-B15	1.69	470.1
117	A29-M-B43	1.66	462.1
118	A29-M-B22	1.61	434.1
119	A15-M-B38	1.52	356.2
120	A15-M-B24	1.48	353.1
121	A15-M-B28	1.5	346.1
122	A15-M-B13	1.48	364.1
123	A15-M-B42	1.3	324.1
124	A15-M-B6	1.5	400.2
125	A24-M-B38	1.35	384.2
126	A24-M-B28	1.33	374.1

Entry	Compound	r.t. (min)	[M+H]+
127	A24-M-B13	1.31	392.1
128	A24-M-B42	1.12	352.1
129	A24-M-B6	1.33	428.2
130	A12-M-B39	1.5	346.1
131	A12-M-B42	1.34	362.1
132	A12-M-B6	1.54	438.1
133	A18-M-B39	1.49	328.1
134	A18-M-B28	1.53	366.1
135	A18-M-B42	1.32	344.1
136	A18-M-B6	1.52	420.1
137	A11-M-B40	1.7	440.1
138	A11-M-B42	1.42	378
139	A11-M-B6	1.61	454.1
140	A31-M-B38	1.47	360.1
141	A31-M-B39	1.4	312.1
142	A31-M-B28	1.45	350.1
143	A31-M-B13	1.43	368.1
144	A31-M-B42	1.24	328.1
145	A31-M-B6	1.45	404.1
146	A29-M-B42	1.4	394.1
147	A29-M-B6	1.58	470.1
148	A36-M-B37	1.55	352.2
149	A36-M-B19	1.26	296.1
150	A36-M-B8	1.47	376.1

Entry	Compound	r.t. (min)	[M+H]+
151	A36-M-B25	1.39	324.1
152	A36-M-B23	1.32	310.1
153	A6-M-B37	1.61	348.2
154	A6-M-B25	1.46	320.2
155	A6-M-B41	1.25	296.1
156	A6-M-B23	1.39	306.2
157	A17-M-B37	1.46	376.2
158	A17-M-B19	1.16	320.1
159	A17-M-B8	1.38	400.2
160	A17-M-B25	1.3	348.2
161	A17-M-B23	1.23	334.2
162	A23-M-B37	1.49	359.2
163	A23-M-B8	1.41	383.1
164	A23-M-B25	1.33	331.2
165	A23-M-B23	1.26	317.1
166	A1-M-B2	1.17	288.1
167	A1-M-B19	1.3	314.1
168	A1-M-B3	1.32	316.1
169	A1-M-B8	1.5	394.1
170	A1-M-B41	1.22	318.1
171	A1-M-B23	1.36	328.1
172	A2-M-B37	1.52	394.2
173	A2-M-B19	1.24	338.1
174	A2-M-B3	1.26	340.2

Entry	Compound	r.t. (min)	[M+H]+
175	A2-M-B8	1.45	418.2
176	A2-M-B25	1.37	366.2
177	A2-M-B41	1.17	342.1
178	A2-M-B23	1.3	352.2
179	A16-M-B3	1.22	305.1
180	A16-M-B23	1.26	317.1
181	A36-M-B32	1.44	376.1
182	A36-M-B4	1.64	422.2
183	A36-M-B44	1.49	376.1
184	A36-M-B29	1.34	322.1
185	A36-M-B11	1.51	362.1
186	A36-M-B18	1.49	350.1
187	A36-M-B17	1.55	366.1
188	A36-M-B14	1.43	422.1
189	A36-M-B10	1.52	392.1
190	A36-M-B9	1.49	386.1
191	A6-M-B4	1.69	418.2
192	A6-M-B44	1.55	372.2
193	A6-M-B29	1.39	318.1
194	A6-M-B33	1.56	334.2
195	A6-M-B11	1.57	358.2
196	A6-M-B18	1.54	346.1
197	A6-M-B17	1.62	362.1
198	A6-M-B14	1.49	418.2

Entry	Compound	r.t. (min)	[M+H]+
199	A6-M-B16	1.75	396.1
200	A6-M-B10	1.58	388.2
201	A6-M-B9	1.54	382.1
202	A17-M-B32	1.35	400.2
203	A17-M-B44	1.41	400.2
204	A17-M-B29	1.24	346.1
205	A17-M-B33	1.41	362.2
206	A17-M-B11	1.42	386.1
207	A17-M-B18	1.39	374.1
208	A17-M-B17	1.47	390.1
209	A17-M-B14	1.34	446.2
210	A17-M-B16	1.6	424.1
211	A17-M-B10	1.43	416.2
212	A17-M-B9	1.4	410.1
213	A23-M-B4	1.58	429.2
214	A23-M-B44	1.44	383.1
215	A23-M-B29	1.27	329.1
216	A23-M-B33	1.44	345.2
217	A23-M-B11	1.45	369.1
218	A23-M-B18	1.42	357.1
219	A23-M-B16	1.64	407
220	A23-M-B9	1.42	393.1
221	A1-M-B44	1.52	394.1
222	A1-M-B11	1.54	380.1

Entry	Compound	r.t. (min)	[M+H]+
223	A1-M-B18	1.52	368.1
224	A1-M-B14	1.46	440.1
225	A1-M-B9	1.51	404.1
226	A2-M-B32	1.42	418.2
227	A2-M-B4	1.61	464.2
228	A2-M-B44	1.47	418.2
229	A2-M-B29	1.32	364.1
230	A2-M-B33	1.47	380.2
231	A2-M-B11	1.48	404.2
232	A2-M-B18	1.46	392.1
233	A2-M-B17	1.52	408.1
234	A2-M-B14	1.41	464.2
235	A2-M-B10	1.49	434.2
236	A2-M-B9	1.46	428.1
237	A16-M-B4	1.58	429.2
238	A16-M-B44	1.44	383.1
239	A16-M-B11	1.45	369.1
240	A16-M-B18	1.42	357.11
241	A16-M-B14	1.37	429.15
242	A16-M-B10	1.46	399.14
243	A16-M-B9	1.42	393.09
244	A36-M-B38	1.45	360.1
245	A36-M-B20	1.49	368.1
246	A36-M-B24	1.41	357.1

Entry	Compound	r.t. (min)	[M+H]+
247	A36-M-B28	1.42	350.1
248	A36-M-B21	1.54	400
249	A36-M-B42	1.22	328.1
250	A36-M-B6	1.43	404.1
251	A36-M-B35	1.39	352.1
252	A6-M-B20	1.55	364.1
253	A6-M-B24	1.47	353.1
254	A6-M-B28	1.49	346.1
255	A6-M-B42	1.28	324.1
256	A6-M-B6	1.49	400.2
257	A17-M-B39	1.27	336.2
258	A17-M-B20	1.39	392.1
259	A17-M-B24	1.31	381.1
260	A17-M-B26	1.31	356.1
261	A17-M-B28	1.33	374.1
262	A17-M-B13	1.31	392.1
263	A17-M-B21	1.43	424.1
264	A17-M-B42	1.13	352.1
265	A17-M-B6	1.34	428.2
266	A23-M-B20	1.43	375.1
267	A23-M-B26	1.34	339.1
268	A23-M-B28	1.36	357.1
269	A23-M-B13	1.34	375.1
270	A23-M-B42	1.15	335.1

Entry	Compound	r.t. (min)	[M+H]+
271	A23-M-B6	1.36	411.1
272	A1-M-B39	1.41	330.1
273	A1-M-B20	1.52	386.1
274	A1-M-B26	1.44	350.1
275	A1-M-B28	1.46	368.1
276	A1-M-B13	1.44	386.1
277	A1-M-B42	1.26	346.1
278	A1-M-B6	1.46	422.1
279	A2-M-B20	1.47	410.1
280	A2-M-B24	1.36	399.1
281	A2-M-B28	1.4	392.1
282	A2-M-B13	1.39	410.1
283	A2-M-B42	1.51	442.1
284	A2-M-B42	1.21	370.1
285	A2-M-B6	1.41	446.2
286	A16-M-B38	1.39	367.2
287	A16-M-B28	1.36	357.1
288	A16-M-B42	1.16	335.1
289	A16-M-B6	1.37	411.1
290	A36-M-B15	1.55	404.1
291	A36-M-B43	1.53	396.1
292	A36-M-B22	1.46	368.1
293	A6-M-B15	1.61	400.1
294	A6-M-B43	1.58	392.1

Entry	Compound	r.t. (min)	[M+H]+
295	A6-M-B22	1.52	364.1
296	A17-M-B15	1.47	428.1
297	A17-M-B43	1.45	420.1
298	A17-M-B22	1.37	392.1
299	A23-M-B15	1.49	411.1
300	A23-M-B22	1.4	375.1
301	A1-M-B15	1.58	422.1
302	A1-M-B43	1.55	414.1
303	A1-M-B1	1.56	547.2
304	A2-M-B15	1.52	446.1
305	A2-M-B12	1.42	426.1
306	A2-M-B43	1.5	438.1
307	A2-M-B27	1.44	380.2
308	A2-M-B22	1.43	410.1
309	A16-M-B15	1.49	411.1
310	A16-M-B22	1.4	375.1
311	A5-M-B37	1.55	394.21
312	A5-M-B19	1.28	338.14
313	A5-M-B3	1.3	340.16
314	A5-M-B8	1.48	418.17
315	A5-M-B25	1.41	366.17
316	A5-M-B23	1.34	352.16
317	A14-M-B2	1.34	280.14
318	A14-M-B37	1.72	362.22

Entry	Compound	r.t. (min)	[M+H]+
319	A14-M-B19	1.45	306.15
320	A14-M-B3	1.48	308.17
321	A14-M-B25	1.58	334.18
322	A14-M-B41	1.39	310.2
323	A14-M-B23	1.51	320.2
324	A34-M-B37	1.64	378.2
325	A34-M-B19	1.37	322.2
326	A34-M-B3	1.4	324.2
327	A34-M-B8	1.57	402.2
328	A34-M-B25	1.5	350.2
329	A34-M-B41	1.32	326.1
330	A34-M-B23	1.44	336.2
331	A7-M-B2	1.25	296.1
332	A7-M-B37	1.63	378.2
333	A7-M-B8	1.56	402.2
334	A7-M-B25	1.49	350.2
335	A7-M-B23	1.43	336.2
336	A9-M-B37	1.69	362.2
337	A9-M-B31	1.53	386.2
338	A9-M-B3	1.45	308.2
339	A9-M-B8	1.62	386.2
340	A9-M-B25	1.55	334.2
341	A9-M-B23	1.49	320.2
342	A10-M-B34	1.55	356.2

Entry	Compound	r.t. (min)	[M+H]+
343	A10-M-B2	1.32	280.1
344	A10-M-B37	1.71	362.2
345	A10-M-B19	1.44	306.2
346	A10-M-B3	1.46	308.2
347	A10-M-B8	1.63	386.2
348	A25-M-B19	1.53	320.2
349	A25-M-B3	1.54	322.2
350	A25-M-B8	1.7	400.2
351	A25-M-B41	1.47	324.2
352	A25-M-B23	1.58	334.2
353	A27-M-B34	1.09	371.2
354	A27-M-B2	0.85	295.2
355	A27-M-B37	1.23	377.2
356	A27-M-B36	0.97	323.2
357	A27-M-B19	0.94	321.2
358	A27-M-B30	0.92	309.2
359	A27-M-B3	0.97	323.2
360	A27-M-B8	1.17	401.2
361	A27-M-B25	1.07	349.2
362	A27-M-B23	1.02	335.2
363	A5-M-B32	1.39	418.2
364	A5-M-B4	1.57	464.2
365	A5-M-B44	1.45	418.2
366	A5-M-B29	1.29	364.1

Entry	Compound	r.t. (min)	[M+H]+
367	A5-M-B33	1.44	380.2
368	A5-M-B11	1.44	404.2
369	A5-M-B18	1.43	392.1
370	A5-M-B17	1.5	408.1
371	A5-M-B14	1.39	464.2
372	A5-M-B9	1.43	428.1
373	A14-M-B32	1.54	386.2
374	A14-M-B44	1.61	386.2
375	A14-M-B29	1.47	332.1
376	A14-M-B33	1.62	348.2
377	A14-M-B11	1.61	372.2
378	A14-M-B18	1.6	360.1
379	A14-M-B17	1.67	376.1
380	A14-M-B14	1.55	432.2
381	A14-M-B9	1.6	396.1
382	A34-M-B4	1.66	448.2
383	A34-M-B44	1.53	402.2
384	A34-M-B29	1.39	348.1
385	A34-M-B33	1.55	364.2
386	A34-M-B11	1.55	388.2
387	A34-M-B18	1.53	376.1
388	A34-M-B17	1.6	392.1
389	A34-M-B14	1.49	448.2
390	A34-M-B10	1.56	418.2

Entry	Compound	r.t. (min)	[M+H]+
391	A34-M-B9	1.51	412.1
392	A7-M-B4	1.65	448.2
393	A7-M-B32	1.46	402.2
394	A7-M-B44	1.52	402.2
395	A7-M-B29	1.37	348.1
396	A7-M-B33	1.53	364.2
397	A7-M-B11	1.54	388.2
398	A7-M-B18	1.51	376.1
399	A7-M-B17	1.57	392.1
400	A7-M-B14	1.47	448.2
401	A7-M-B9	1.49	412.1
402	A9-M-B32	1.52	386.2
403	A9-M-B4	1.71	432.2
404	A9-M-B29	1.44	332.1
405	A9-M-B33	1.6	348.2
406	A9-M-B18	1.57	360.1
407	A9-M-B17	1.64	376.1
408	A9-M-B14	1.52	432.2
409	A9-M-B16	1.76	410.1
410	A9-M-B9	1.56	396.1
411	A10-M-B44	1.57	386.18
412	A10-M-B29	1.45	332.13
413	A10-M-B11	1.59	372.16
414	A10-M-B18	1.57	360.14

Entry	Compound	r.t. (min)	[M+H]+
415	A10-M-B14	1.53	432.18
416	A25-M-B29	1.52	346.15
417	A25-M-B11	1.68	386.18
418	A25-M-B14	1.59	446.2
419	A25-M-B9	1.64	410.14
420	A27-M-B32	1.09	401.19
421	A27-M-B4	1.28	447.21
422	A27-M-B44	1.15	401.19
423	A27-M-B29	0.98	347.14
424	A27-M-B33	1.12	363.21
425	A27-M-B11	1.12	387.17
426	A27-M-B17	1.17	391.12
427	A27-M-B14	1.07	447.2
428	A27-M-B16	1.27	425.1
429	A27-M-B9	1.12	411.1
430	A5-M-B15	1.54	446.1
431	A5-M-B12	1.46	426.1
432	A5-M-B43	1.53	438.1
433	A5-M-B22	1.47	410.1
434	A14-M-B12	1.62	394.1
435	A14-M-B43	1.67	406.1
436	A14-M-B22	1.62	378.1
437	A34-M-B15	1.64	430.1
438	A34-M-B12	1.54	410.1

Entry	Compound	r.t. (min)	[M+H]+
439	A34-M-B43	1.6	422.1
440	A34-M-B22	1.57	394.1
441	A7-M-B12	1.54	410.1
442	A7-M-B15	1.64	430.1
443	A7-M-B43	1.61	422.1
444	A7-M-B22	1.56	394.1
445	A9-M-B15	1.69	414.1
446	A9-M-B12	1.59	394.1
447	A9-M-B43	1.65	406.1
448	A9-M-B27	1.61	348.2
449	A9-M-B22	1.6	378.1
450	A10-M-B15	1.71	414.1
451	A10-M-B12	1.61	394.1
452	A10-M-B43	1.67	406.1
453	A10-M-B22	1.63	378.1
454	A25-M-B15	1.78	428.1
455	A25-M-B43	1.75	420.1
456	A25-M-B22	1.71	392.2
457	A27-M-B15	1.24	429.1
458	A27-M-B43	1.24	421.1
459	A27-M-B22	1.14	393.1
460	A5-M-B38	1.46	402.2
461	A5-M-B20	1.49	410.1
462	A5-M-B24	1.42	399.1

Entry	Compound	r.t. (min)	[M+H]+
463	A5-M-B28	1.44	392.1
464	A5-M-B13	1.43	410.1
465	A5-M-B42	1.25	370.1
466	A5-M-B6	1.45	446.2
467	A5-M-B35	1.39	394.1
468	A14-M-B24	1.58	367.2
469	A14-M-B28	1.6	360.1
470	A14-M-B13	1.58	378.1
471	A14-M-B21	1.69	410.1
472	A14-M-B42	1.42	338.1
473	A14-M-B6	1.59	414.2
474	A14-M-B35	1.55	362.1
475	A34-M-B20	1.59	394.1
476	A34-M-B24	1.51	383.1
477	A34-M-B13	1.52	376.1
478	A34-M-B13	1.51	394.1
479	A34-M-B21	1.62	426.1
480	A34-M-B42	1.35	354.1
481	A34-M-B6	1.53	430.2
482	A34-M-B35	1.49	378.1
483	A7-M-B20	1.57	394.1
484	A7-M-B24	1.5	383.1
485	A7-M-B28	1.52	376.1
486	A7-M-B13	1.49	394.1

Entry	Compound	r.t. (min)	[M+H]+
487	A7-M-B21	1.59	426.1
488	A7-M-B42	1.34	354.1
489	A7-M-B6	1.52	430.2
490	A9-M-B38	1.58	370.2
491	A9-M-B39	1.53	322.2
492	A9-M-B20	1.62	378.1
493	A9-M-B24	1.54	367.2
494	A9-M-B26	1.55	342.2
495	A9-M-B28	1.57	360.1
496	A9-M-B13	1.56	378.1
497	A9-M-B21	1.65	410.1
498	A9-M-B42	1.39	338.1
499	A9-M-B6	1.58	414.2
500	A9-M-B35	1.53	362.1
501	A10-M-B20	1.65	378.1
502	A10-M-B28	1.57	360.1
503	A10-M-B13	1.55	378.1
504	A10-M-B21	1.67	410.1
505	A10-M-B6	1.58	414.2
506	A25-M-B40	1.72	414.2
507	A25-M-B20	1.72	392.2
508	A25-M-B24	1.64	381.2
509	A25-M-B26	1.64	356.2
510	A25-M-B28	1.67	374.2

Entry	Compound	r.t. (min)	[M+H]+
511	A25-M-B13	1.64	392.2
512	A25-M-B42	1.47	352.2
513	A25-M-B6	1.65	428.2
514	A27-M-B39	1.07	337.2
515	A27-M-B20	1.18	393.1
516	A27-M-B24	1.09	382.2
517	A27-M-B28	1.09	375.2
518	A27-M-B42	0.93	353.2
519	A27-M-B6	1.14	429.2
520	A27-M-B35	1.09	377.1
521	A30-M-B2	1.35	312.1
522	A30-M-B37	1.71	394.2
523	A30-M-B36	1.47	340.1
524	A30-M-B3	1.47	340.1
525	A30-M-B8	1.6	418.2
526	A30-M-B41	1.4	342.1
527	A30-M-B23	1.51	352.1
528	A3-M-B37	1.72	406.2
529	A3-M-B19	1.49	350.2
530	A3-M-B3	1.48	352.2
531	A3-M-B8	1.64	430.2
532	A3-M-B25	1.59	378.2
533	A3-M-B41	1.44	354.2
534	A3-M-B23	1.54	364.2

Entry	Compound	r.t. (min)	[M+H]+
535	A8-M-B37	1.61	380.2
536	A8-M-B31	1.45	404.1
537	A8-M-B36	1.37	326.1
538	A8-M-B19	1.35	324.1
539	A8-M-B3	1.37	326.1
540	A8-M-B8	1.53	404.1
541	A8-M-B25	1.46	352.1
542	A8-M-B41	1.29	328.1
543	A8-M-B23	1.4	338.1
544	A33-M-B37	1.71	418.2
545	A33-M-B36	1.49	364.1
546	A33-M-B3	1.49	364.1
547	A33-M-B8	1.6	442.1
548	A33-M-B25	1.57	390.1
549	A20-M-B34	1.54	356.2
550	A20-M-B2	1.31	280.1
551	A20-M-B37	1.67	362.2
552	A20-M-B36	1.45	308.2
553	A20-M-B19	1.43	306.2
554	A20-M-B3	1.46	308.2
555	A20-M-B8	1.61	386.2
556	A20-M-B25	1.54	334.2
557	A20-M-B41	1.37	310.2
558	A20-M-B23	1.48	320.2

Entry	Compound	r.t. (min)	[M+H]+
559	A4-M-B2	1.21	288.1
560	A4-M-B37	1.59	370.2
561	A4-M-B31	1.44	394.1
562	A4-M-B36	1.35	316.1
563	A4-M-B19	1.33	314.1
564	A4-M-B3	1.35	316.1
565	A4-M-B8	1.47	394.1
566	A4-M-B25	1.44	342.1
567	A4-M-B41	1.26	318.1
568	A4-M-B23	1.38	328.1
569	A13-M-B2	1.23	288.1
570	A13-M-B37	1.61	370.2
571	A13-M-B8	1.53	394.1
572	A13-M-B41	1.29	318.1
573	A13-M-B23	1.41	328.1
574	A21-M-B2	1.21	300.1
575	A21-M-B37	1.57	382.2
576	A21-M-B19	1.31	326.1
577	A21-M-B3	1.34	328.1
578	A21-M-B8	1.5	406.2
579	A21-M-B25	1.43	354.2
580	A21-M-B41	1.25	330.1
581	A21-M-B23	1.35	340.1
582	A30-M-B29	1.44	364.1

Entry	Compound	r.t. (min)	[M+H]+
583	A30-M-B33	1.58	380.2
584	A30-M-B14	1.52	464.2
585	A30-M-B10	1.61	434.2
586	A30-M-B9	1.55	428.1
587	A3-M-B32	1.53	430.2
588	A3-M-B4	1.71	476.2
589	A3-M-B29	1.46	376.2
590	A3-M-B33	1.6	392.2
591	A3-M-B11	1.61	416.2
592	A3-M-B17	1.65	420.1
593	A3-M-B14	1.54	476.2
594	A3-M-B16	1.79	454.1
595	A3-M-B10	1.62	446.2
596	A3-M-B9	1.59	440.2
597	A8-M-B32	1.43	404.1
598	A8-M-B4	1.61	450.2
599	A8-M-B44	1.48	404.1
600	A8-M-B33	1.49	366.2
601	A8-M-B11	1.5	390.1
602	A8-M-B17	1.54	394.1
603	A8-M-B14	1.42	450.1
604	A8-M-B16	1.66	428
605	A8-M-B10	1.5	420.1
606	A8-M-B9	1.47	414.1

Entry	Compound	r.t. (min)	[M+H]+
607	A33-M-B4	1.69	488.2
608	A33-M-B44	1.57	442.1
609	A33-M-B29	1.44	388.08
610	A33-M-B33	1.58	404.15
611	A33-M-B14	1.52	488.14
612	A33-M-B10	1.6	458.12
613	A33-M-B9	1.56	452.08
614	A20-M-B32	1.5	386.18
615	A20-M-B4	1.68	432.2
616	A20-M-B44	1.55	386.18
617	A20-M-B29	1.42	332.13
618	A20-M-B17	1.62	376.11
619	A20-M-B14	1.5	432.18
620	A20-M-B16	1.76	410.07
621	A20-M-B9	1.55	396.12
622	A4-M-B32	1.41	394.13
623	A4-M-B4	1.59	440.15
624	A4-M-B29	1.31	340.08
625	A4-M-B33	1.47	356.15
626	A4-M-B14	1.4	440.13
627	A4-M-B9	1.44	404.1
628	A13-M-B44	1.48	394.1
629	A13-M-B29	1.34	340.1
630	A13-M-B11	1.5	380.1

Entry	Compound	r.t. (min)	[M+H]+
631	A13-M-B17	1.53	384.1
632	A13-M-B14	1.42	440.1
633	A13-M-B9	1.47	404.1
634	A21-M-B32	1.39	406.2
635	A21-M-B4	1.56	452.2
636	A21-M-B44	1.45	406.2
637	A21-M-B29	1.3	352.1
638	A21-M-B33	1.45	368.2
639	A21-M-B11	1.46	392.1
640	A21-M-B17	1.5	396.1
641	A21-M-B14	1.39	452.2
642	A21-M-B10	1.46	422.1
643	A21-M-B9	1.43	416.1
644	A30-M-B15	1.7	446.1
645	A30-M-B22	1.62	410.1
646	A3-M-B15	1.72	458.1
647	A3-M-B43	1.7	450.2
648	A3-M-B27	1.65	392.2
649	A3-M-B22	1.64	422.2
650	A8-M-B15	1.59	432.1
651	A8-M-B43	1.57	424.1
652	A8-M-B27	1.51	366.2
653	A8-M-B22	1.51	396.1
654	A33-M-B15	1.69	470.1

Entry	Compound	r.t. (min)	[M+H]+
655	A33-M-B43	1.66	462.1
656	A33-M-B22	1.61	434.1
657	A20-M-B15	1.68	414.1
658	A20-M-B12	1.58	394.1
659	A20-M-B43	1.65	406.1
660	A20-M-B27	1.6	348.2
661	A20-M-B1	1.64	539.2
662	A20-M-B22	1.6	378.1
663	A4-M-B15	1.58	422.1
664	A4-M-B12	1.47	402.1
665	A4-M-B22	1.49	386.1
666	A13-M-B15	1.59	422.1
667	A13-M-B43	1.57	414.1
668	A13-M-B22	1.51	386.1
669	A21-M-B15	1.56	434.1
670	A21-M-B43	1.54	426.1
671	A21-M-B22	1.47	398.1
672	A30-M-B13	1.56	410.1
673	A30-M-B42	1.39	370.1
674	A30-M-B6	1.57	446.2
675	A3-M-B38	1.63	414.2
676	A3-M-B39	1.57	366.2
677	A3-M-B20	1.66	422.2
678	A3-M-B24	1.59	411.2

Entry	Compound	r.t. (min)	[M+H]+
679	A3-M-B26	1.59	386.2
680	A3-M-B28	1.61	404.2
681	A3-M-B13	1.59	422.2
682	A3-M-B21	1.71	454.1
683	A3-M-B42	1.42	382.2
684	A3-M-B6	1.61	458.2
685	A3-M-B35	1.57	406.2
686	A8-M-B38	1.49	388.1
687	A8-M-B20	1.53	396.1
688	A8-M-B24	1.45	385.1
689	A8-M-B28	1.47	378.1
690	A8-M-B13	1.45	396.1
691	A8-M-B21	1.58	428
692	A8-M-B42	1.27	356.1
693	A8-M-B6	1.47	432.1
694	A8-M-B35	1.43	380.1
695	A33-M-B20	1.63	434.1
696	A33-M-B24	1.55	423.1
697	A33-M-B28	1.58	416.1
698	A33-M-B13	1.56	434.1
699	A33-M-B42	1.39	394.1
700	A33-M-B6	1.57	470.1
701	A20-M-B38	1.58	370.2
702	A20-M-B39	1.52	322.2

Entry	Compound	r.t. (min)	[M+H]+
703	A20-M-B20	1.62	378.1
704	A20-M-B24	1.54	367.2
705	A20-M-B26	1.54	342.2
706	A20-M-B28	1.56	360.1
707	A20-M-B13	1.54	378.1
708	A20-M-B42	1.36	338.1
709	A20-M-B6	1.56	414.2
710	A20-M-B35	1.51	362.1
711	A4-M-B38	1.48	378.1
712	A4-M-B39	1.41	330.1
713	A4-M-B26	1.43	350.1
714	A4-M-B28	1.46	368.1
715	A4-M-B13	1.43	386.1
716	A4-M-B21	1.55	418
717	A4-M-B42	1.25	346.1
718	A4-M-B6	1.46	422.1
719	A13-M-B13	1.46	386.1
720	A13-M-B6	1.48	422.1
721	A21-M-B38	1.46	390.2
722	A21-M-B20	1.49	398.1
723	A21-M-B24	1.42	387.1
724	A21-M-B28	1.44	380.1
725	A21-M-B13	1.42	398.1
726	A21-M-B42	1.24	358.1

Entry	Compound	r.t. (min)	[M+H]+
727	A21-M-B6	1.44	434.1
728	A21-M-B35	1.4	382.1
729	A38-M-B15	1.53	392
730	A38-M-B22	1.44	356.1
731	A37-M-B15	1.54	416.1
732	A37-M-B43	1.52	408.1
733	A37-M-B27	1.45	350.2
734	A37-M-B22	1.45	380.1
735	A22-M-B15	1.63	400.1
736	A22-M-B43	1.59	392.1
737	A22-M-B27	1.54	334.2
738	A22-M-B22	1.54	364.1
739	A35-M-B15	1.55	386.1
740	A35-M-B43	1.53	378.1
741	A35-M-B27	1.46	320.2
742	A35-M-B22	1.46	350.1
743	A39-M-B22	1.42	356.1
744	A19-M-B15	1.54	416.1
745	A19-M-B43	1.53	408.1
746	A19-M-B27	1.46	350.2
747	A19-M-B1	1.53	541.2
748	A19-M-B22	1.46	380.1
749	A26-M-B15	1.56	404.1
750	A26-M-B43	1.54	396.1

Entry	Compound	r.t. (min)	[M+H]+
751	A26-M-B22	1.48	368.1
752	A28-M-B22	1.45	380.1
753	A28-M-B2	1.17	282.1
754	A28-M-B37	1.56	364.2
755	A28-M-B36	1.31	310.2
756	A28-M-B19	1.28	308.1
757	A28-M-B30	1.24	296.1
758	A28-M-B3	1.31	310.2
759	A28-M-B8	1.49	388.2
760	A28-M-B25	1.41	336.2
761	A28-M-B41	1.22	312.1
762	A26-M-B34	1.44	346.1
763	A26-M-B2	1.2	270.1
764	A26-M-B37	1.59	352.2
765	A26-M-B31	1.43	376.1
766	A26-M-B36	1.34	298.1
767	A26-M-B19	1.32	296.1
768	A26-M-B30	1.27	284.1
769	A26-M-B3	1.34	298.1
770	A26-M-B8	1.52	376.1
771	A26-M-B25	1.44	324.1
772	A26-M-B41	1.25	300.1
773	A19-M-B34	1.42	358.2
774	A19-M-B2	1.18	282.1

Entry	Compound	r.t. (min)	[M+H]+
775	A19-M-B37	1.57	364.2
776	A19-M-B36	1.32	310.2
777	A19-M-B19	1.3	308.1
778	A19-M-B30	1.25	296.1
779	A19-M-B3	1.32	310.2
780	A19-M-B8	1.49	388.2
781	A19-M-B25	1.42	336.2
782	A19-M-B41	1.23	312.1
783	A39-M-B2	1.14	258.1
784	A39-M-B37	1.52	340.1
785	A39-M-B36	1.28	286.1
786	A39-M-B19	1.25	284.1
787	A39-M-B30	1.21	272.1
788	A39-M-B3	1.28	286.1
789	A39-M-B8	1.46	364.1
790	A39-M-B25	1.39	312.1
791	A35-M-B2	1.18	252.1
792	A35-M-B37	1.57	334.2
793	A35-M-B36	1.33	280.1
794	A35-M-B19	1.29	278.1
795	A35-M-B30	1.25	266.1
796	A35-M-B3	1.32	280.1
797	A35-M-B8	1.5	358.2
798	A35-M-B25	1.43	306.2

Entry	Compound	r.t. (min)	[M+H]+
799	A35-M-B41	1.23	282.1
800	A22-M-B34	1.49	342.2
801	A22-M-B2	1.27	266.1
802	A22-M-B37	1.64	348.2
803	A22-M-B36	1.4	294.2
804	A22-M-B19	1.37	292.1
805	A22-M-B30	1.33	280.1
806	A22-M-B3	1.4	294.2
807	A22-M-B8	1.57	372.2
808	A22-M-B25	1.5	320.2
809	A22-M-B41	1.32	296.1
810	A37-M-B2	1.18	282.1
811	A37-M-B37	1.55	364.2
812	A37-M-B36	1.31	310.2
813	A37-M-B19	1.29	308.1
814	A37-M-B30	1.24	296.1
815	A37-M-B3	1.31	310.2
816	A37-M-B8	1.49	388.2
817	A37-M-B25	1.41	336.2
818	A37-M-B41	1.22	312.1
819	A38-M-B2	1.14	258.1
820	A38-M-B37	1.54	340.1
821	A38-M-B36	1.29	286.1
822	A38-M-B19	1.27	284.1

Entry	Compound	r.t. (min)	[M+H]+
823	A38-M-B3	1.29	286.1
824	A38-M-B8	1.47	364.1
825	A38-M-B25	1.39	312.1
826	A38-M-B41	1.2	288.1
827	A28-M-B23	1.36	322.2
828	A28-M-B32	1.42	388.2
829	A28-M-B4	1.6	434.18
830	A28-M-B29	1.33	334.11
831	A28-M-B33	1.48	350.2
832	A26-M-B23	1.39	310.13
833	A26-M-B32	1.44	376.1
834	A26-M-B4	1.64	422.16
835	A26-M-B44	1.51	376.14
836	A26-M-B29	1.36	322.1
837	A26-M-B33	1.52	338.2
838	A19-M-B23	1.37	322.2
839	A19-M-B32	1.43	388.2
840	A19-M-B4	1.62	434.2
841	A19-M-B5	1.57	386.18
842	A19-M-B44	1.49	388.16
843	A19-M-B29	1.34	334.11
844	A19-M-B33	1.49	350.18
845	A19-M-B7	1.39	324.16
846	A39-M-B23	1.33	298.09

Entry	Compound	r.t. (min)	[M+H]+
847	A39-M-B32	1.4	364.1
848	A39-M-B4	1.59	410.12
849	A39-M-B44	1.46	364.1
850	A39-M-B29	1.3	310.06
851	A39-M-B33	1.46	326.12
852	A35-M-B23	1.37	292.14
853	A35-M-B4	1.62	404.17
854	A35-M-B44	1.49	358.15
855	A35-M-B29	1.34	304.1
856	A35-M-B7	1.39	294.15
857	A22-M-B23	1.45	306.15
858	A22-M-B4	1.68	418.18
859	A22-M-B44	1.56	372.16
860	A22-M-B29	1.41	318.12
861	A22-M-B33	1.57	334.18
862	A37-M-B23	1.36	322.15
863	A37-M-B32	1.42	388.16

Entry	Compound	r.t. (min)	[M+H]+
864	A37-M-B4	1.61	434.18
865	A37-M-B44	1.48	388.16
866	A37-M-B29	1.33	334.11
867	A37-M-B33	1.47	350.18
868	A38-M-B23	1.35	298.09
869	A38-M-B32	1.4	364.1
870	A38-M-B4	1.6	410.12
871	A38-M-B44	1.47	364.1
872	A38-M-B29	1.31	310.06

Example 7

N-isopropyl-N'-[6-(4-methoxyphenyl)-1H-indazol-3-yl]urea

The reaction was performed in a "Miniblock" reactor (Bohdan) charged with trityl-resin bearing 6-(4-methoxyphenyl)-1H-indazol-3-amine, obtained according to the procedure previously described.

To resin (70 mg) bearing 6-(4-methoxyphenyl)-1H-indazol-3-amine (1.2 mmol/g) was added isopropyl isocyanate (0.2 mmol) in pyridine (2 ml). The reaction mixture was shaken for 48 hours at 55°C.

The resin was washed as follows:

5x a) 1 ml DMF; b) 1 ml H_2O

The resulting imids of 6-(4-methoxyphenyl)-1H-indazol-3-amine could be either isolated or converted to amids using an appropriate base such as aqueous ammonia. The ammonia treatment could be performed prior or post cleavage from the resin:

Aqueous NH_4OH (20%) was dissolved in ice cold dioxane to afford a solution ammonia/dioxane 1:4 V/V. This solution was added to the appropriate reactor, which was then sealed and agitated at 55°C for 48 hours. The resins were then washed

5x a) 1 ml DMF; b) 1 ml H_2O

5x a) 1 ml MeOH; b) 1 ml DCM

5x a) 1 ml DCM

The cleavage was performed the following way:

1x 0.5 ml 20% TFA/DCM 5 min.

4x 0.2 ml 20% TFA/DCM 2 min.

The cleavage solutions were combined and then dried. The solid, was taken up in dimethylsulfoxyde and filtered to remove particular matter. The cleared DMSO solution was subjected to preparative reverse phase HPLC (C-18) using the instrument 1 (see above)

The product fractions were collected and those containing product pooled. Evaporation of the solvent then gave the dried N-isopropyl-N'-[6-(4-methoxyphenyl)-1H-indazol-3-yl]urea as a dried powder HPLC r.t. (Method I): 5.61; $[M+H]^+ = 325.33$

The cleavage solutions were combined and then dried.

By working in an analogous way, starting from 6-aryl-1H-indazol-3-amines derivatives (obtained according to the procedure for 6-(4-methoxyphenyl)-1H-indazol-3-amine), the following products were cleaved from the resin:

ethyl N-({[6-(3-methoxyphenyl)-1H-indazol-3-yl]amino}carbonyl)glycinate HPLC r.t. (Method I); 5.26; $[M+H]^+ = 369.29$

N-ethyl-N'-[6-(3-methoxyphenyl)-1H-indazol-3-yl]urea HPLC r.t. (Method I): 5.14; $[M+H]^+ = 311.33$

N-[6-(3-methoxyphenyl)-1H-indazol-3-yl]-N'-propylurea HPLC r.t. (Method I): 5.66; $[M+H]^+ = 325.33$

N-{3-[3-({[(2-methoxyphenyl)amino]carbonyl}amino)-1H-indazol-6-yl]phenyl}acetamide HPLC r.t. (Method I): 5.57; $[M+H]^+ = 416.28$

ethyl N-[({6-[3-(acetylamino)phenyl]-1H-indazol-3-yl}amino)carbonyl]glycinate HPLC r.t. (Method I): 4.17; $[M+H]^+ = 396.3$

ethyl N-({[6-(3-fluorophenyl)-1H-indazol-3-yl]amino}carbonyl)glycinate HPLC r.t. (Method I): 5.45; $[M+H]^+ = 357.28$

N-[6-(3-fluorophenyl)-1H-indazol-3-yl]-N'-propylurea HPLC r.t. (Method I): 5.88; $[M+H]^+ = 313.35$

N-[6-(2-fluorophenyl)-1H-indazol-3-yl]-N'-isopropylurea HPLC r.t. (Method I): 5.7; $[M+H]^+ = 313.35$

ethyl N-({[6-(2-fluorophenyl)-1H-indazol-3-yl]amino}carbonyl)glycinate HPLC r.t. (Method I): 5.33; $[M+H]^+ = 357.28$

N-ethyl-N'-[6-(2-fluorophenyl)-1H-indazol-3-yl]urea HPLC r.t. (Method I): 5.21; $[M+H]^+ = 299.34$

N-[6-(2-fluorophenyl)-1H-indazol-3-yl]-N'-propylurea HPLC r.t. (Method I): 5.76; $[M+H]^+ = 313.35$

N-{6-[4-(hydroxymethyl)phenyl]-1H-indazol-3-yl}-N'-isopropylurea HPLC r.t. (Method I): 4.17; $[M+H]^+ = 325.33$

N-ethyl-N'-{6-[4-(hydroxymethyl)phenyl]-1H-indazol-3-yl}urea HPLC r.t. (Method I): 3.7; $[M+H]^+ = 311.31$

N-{6-[4-(hydroxymethyl)phenyl]-1H-indazol-3-yl}-N'-propylurea HPLC r.t. (Method I): 4.48; $[M+H]^+ = 325.33$

Example 8

N-butyl-N'-[6-(4-fluorophenyl)-1H-indazol-3-yl]urea

The reaction was performed in a "Miniblock" reactor (Bohdan) charged with trityl-resin bearing 6-(4-fluorophenyl)-1H-indazol-3-amine, obtained according to the procedure previously described.

To the resin (9.0 g, 0.7 mmol/g, 6.3 mmol) in anhydrous DCM (100 ml) was added triethylamine (6.363 g, 63.0 mmol) and phenylchloroformate (9.860 g, 63 mmol). The reaction mixture was shaken at room temperature for 18h and the resin isolated by filtration. The resin was washed sequentially with DMF (50 ml), DCM (50 ml), DMF (50

ml), DCM (50 ml), MeOH (50 ml), DCM (50 ml), MeOH (50 ml), DCM (50 ml), MeOH (50 ml), TBME (50 ml x 2) and dried *in vacuo* to give the resin-bound phenyl carbamate (9.90 g, >100 % recovery). 75 mg of the resin (75 mg, 0.0525 mmol) in anhydrous DCM (1 ml) was added *n*-butylamine (38.4 mg, 0.525 mmol). The reaction mixture was shaken at room temperature for 72 hours and then isolated by filtration. The resin was washed sequentially with DMF (1 ml), DCM (1 ml), DMF (1 ml), DCM (1 ml), MeOH (1 ml), DCM (1 ml), MeOH (1 ml), DCM (1 ml), MeOH (1 ml), TBME (1 ml x 2) and dried *in vacuo* to give the resin-bound urea.

The cleavage was performed the following way:

1x 0.5 ml 20% TFA/DCM 5 min.

4x 0.2 ml 20% TFA/DCM 2 min.

The cleavage solutions were combined and then dried. The solid, was taken up in dimethylsulfoxyde and filtered to remove particular matter. The cleared DMSO solution was subjected to preparative reverse phase HPLC (C-18) using the instrument 1 (see above)

The product fractions were collected and those containing product pooled. Evaporation of the solvent then gave the dried N-butyl-N'-[6-(4-fluorophenyl)-1H-indazol-3-yl]urea as a dried powder HPLC r.t. (Method II): 1.43; $[M+H]^+ = 327$

By following the same procedure the following compounds have been synthesized.

By proceeding in the same way (example 8), 176 products were synthesized in parallel and coded in table XI, as formerly indicated; related HPLC retention time (Method II) and the experimentally found [M+H]+ are reported.

Table XI

Entry	Compound	r.t. (min)	[M+H]+
1	A28-M-C3	1.31	351.2
2	A28-M-C21	1.39	339.2
3	A28-M-C15	1.08	396.2
4	A28-M-C13	1.09	391.2
5	A28-M-C8	1.25	367.2
6	A28-M-C9	1.44	387.2
7	A28-M-C12	1.5	401.2
8	A28-M-C22	1.32	325.2

Entry	Compound	r.t. (min)	[M+H]+
9	A28-M-C16	1.38	339.2
10	A28-M-C7	1.33	337.2
11	A28-M-C24	1.09	394.2
12	A19-M-C3	1.32	351.2
13	A19-M-C21	1.4	339.2
14	A19-M-C15	1.09	396.2
15	A19-M-C13	1.09	391.2
16	A19-M-C5	1.02	352.2

Entry	Compound	r.t. (min)	[M+H]+
17	A19-M-C8	1.27	367.2
18	A19-M-C9	1.45	387.2
19	A19-M-C12	1.51	401.2
20	A19-M-C16	1.39	339.2
21	A19-M-C7	1.34	337.2
22	A19-M-C24	1.11	394.2
23	A39-M-C3	1.27	327.1
24	A39-M-C15	1.05	372.1
25	A39-M-C13	1.06	367.1
26	A39-M-C5	0.98	328.1
27	A39-M-C8	1.22	343.1
28	A39-M-C9	1.44	363.1
29	A39-M-C12	1.48	377.1
30	A39-M-C22	1.29	301.1
31	A39-M-C16	1.35	315.1
32	A39-M-C7	1.3	313.1
33	A39-M-C24	1.07	370.2
34	A22-M-C3	1.39	335.2
35	A22-M-C21	1.47	323.2
36	A22-M-C15	1.15	380.2
37	A22-M-C13	1.17	375.2
38	A22-M-C5	1.08	336.2
39	A22-M-C12	1.59	385.2
40	A22-M-C22	1.4	309.2
41	A22-M-C16	1.47	323.2
42	A22-M-C7	1.42	321.2
43	A22-M-C24	1.17	378.2
44	A37-M-C21	1.39	339.2
45	A37-M-C15	1.08	396.2
46	A37-M-C13	1.09	391.2
47	A37-M-C5	1.02	352.2
48	A37-M-C8	1.26	367.2
49	A37-M-C9	1.45	387.2
50	A37-M-C12	1.5	401.2
51	A37-M-C22	1.32	325.2
52	A37-M-C16	1.39	339.2

Entry	Compound	r.t. (min)	[M+H]+
53	A37-M-C7	1.34	337.2
54	A37-M-C24	1.11	394.2
55	A15-M-C3	1.39	335.2
56	A15-M-C21	1.48	323.2
57	A15-M-C15	1.16	380.2
58	A15-M-C13	1.17	375.2
59	A15-M-C5	1.09	336.2
60	A15-M-C9	1.53	371.2
61	A15-M-C22	1.41	309.2
62	A15-M-C16	1.47	323.2
63	A15-M-C24	1.17	378.2
64	A32-M-C3	1.11	378.2
65	A32-M-C21	1.19	366.2
66	A32-M-C15	0.9	423.2
67	A32-M-C13	0.92	418.2
68	A32-M-C8	1.05	394.2
69	A32-M-C9	1.25	414.2
70	A32-M-C12	1.32	428.2
71	A32-M-C22	1.11	352.2
72	A32-M-C7	1.13	364.2
73	A32-M-C24	0.92	421.2
74	A28-M-C19	1.39	365.2
75	A28-M-C25	1.01	366.2
76	A28-M-C33	1.16	408.2
77	A28-M-C27	1.06	340.2
78	A28-M-C28	1.04	326.2
79	A28-M-C35	1.07	367.2
80	A28-M-C36	1.12	341.2
81	A28-M-C11	1.08	388.2
82	A28-M-C14	1.12	394.2
83	A28-M-C2	1.21	337.2
84	A28-M-C32	1.09	368.2
85	A28-M-C30	1.09	394.2
86	A19-M-C19	1.41	365.2
87	A19-M-C25	1.03	366.2
88	A19-M-C33	1.17	408.2

Entry	Compound	r.t. (min)	[M+H]+
89	A19-M-C35	1.11	367.2
90	A19-M-C36	1.15	341.2
91	A19-M-C11	1.12	388.2
92	A19-M-C14	1.15	394.2
93	A19-M-C2	1.23	337.2
94	A19-M-C32	1.13	368.2
95	A19-M-C30	1.12	394.2
96	A39-M-C19	1.37	341.1
97	A39-M-C25	1.01	342.1
98	A39-M-C33	1.15	384.1
99	A39-M-C27	1.06	316.1
100	A39-M-C28	1.04	302.1
101	A39-M-C35	1.07	343.1
102	A39-M-C36	1.11	317.1
103	A39-M-C11	1.08	364.1
104	A39-M-C14	1.12	370.2
105	A39-M-C2	1.19	313.1
106	A39-M-C32	1.09	344.1
107	A39-M-C30	1.08	370.1
108	A22-M-C19	1.48	349.2
109	A22-M-C25	1.12	350.2
110	A22-M-C33	1.25	392.2
111	A22-M-C27	1.16	324.2
112	A22-M-C28	1.14	310.2
113	A22-M-C35	1.18	351.2
114	A22-M-C36	1.23	325.2
115	A22-M-C11	1.18	372.2
116	A22-M-C14	1.23	378.2
117	A22-M-C2	1.3	321.2
118	A22-M-C32	1.2	352.2
119	A22-M-C30	1.19	378.2
120	A37-M-C19	1.4	365.2
121	A37-M-C25	1.05	366.2
122	A37-M-C33	1.18	408.2
123	A37-M-C27	1.1	340.2
124	A37-M-C28	1.08	326.2

Entry	Compound	r.t. (min)	[M+H]+
125	A37-M-C35	1.11	367.2
126	A37-M-C36	1.15	341.2
127	A37-M-C11	1.12	388.2
128	A37-M-C14	1.15	394.2
129	A37-M-C2	1.22	337.2
130	A37-M-C32	1.12	368.2
131	A37-M-C30	1.11	394.2
132	A38-M-C28	1.04	302.1
133	A15-M-C19	1.48	349.2
134	A15-M-C25	1.12	350.2
135	A15-M-C33	1.25	392.2
136	A15-M-C27	1.16	324.2
137	A15-M-C28	1.14	310.2
138	A15-M-C35	1.18	351.2
139	A15-M-C36	1.22	325.2
140	A15-M-C11	1.19	372.2
141	A15-M-C14	1.23	378.2
142	A15-M-C2	1.3	321.2
143	A15-M-C32	1.19	352.2
144	A15-M-C30	1.18	378.2
145	A32-M-C19	1.21	392.2
146	A32-M-C33	1	435.2
147	A32-M-C27	0.91	367.2
148	A32-M-C28	0.9	353.2
149	A32-M-C35	0.93	394.2
150	A32-M-C36	0.96	368.2
151	A32-M-C11	0.93	415.2
152	A32-M-C14	0.96	421.2
153	A32-M-C32	0.94	395.2
154	A28-M-C26	1.23	355.2
155	A28-M-C20	1.39	365.2
156	A28-M-C4	1.07	429.2
157	A28-M-C1	1.53	441.2
158	A28-M-C23	1.13	394.2
159	A28-M-C31	1.19	446.2
160	A28-M-C10	1.39	393.1

Entry	Compound	r.t. (min)	[M+H]+
161	A28-M-C34	1.1	395.2
162	A28-M-C6	1.27	369.1
163	A19-M-C26	1.25	355.2
164	A19-M-C20	1.4	365.2
165	A19-M-C17	1.45	353.2
166	A19-M-C4	1.09	429.2
167	A19-M-C1	1.56	441.2
168	A19-M-C29	1.26	450.2
169	A19-M-C18	1.47	379.2
170	A19-M-C23	1.14	394.2

Entry	Compound	r.t. (min)	[M+H]+
171	A19-M-C31	1.22	446.2
172	A19-M-C10	1.42	393.1
173	A19-M-C34	1.12	395.2
174	A19-M-C6	1.29	369.1
175	A39-M-C26	1.2	331.1
176	A39-M-C20	1.34	341.1

Example 9

N-(6-bromo-1H-indazol-3-yl)-3-chloropropane-1-sulfonamide

The reaction was performed in a "Miniblock" reactor (Bohdan) charged with Trityl-resin bearing 6-bromo-1H-indazol-3-amine. To the resin (12.5 mg) bearing 6-bromo-1H-indazol-3-amine (1.2 mmol/g) was added a 3-chloropropanesulfonyl chloride (0.2 Mol) in pyridine (2 ml). The reaction mixture was shaken for 24 hours at 55°C.

The resin was washed as follows:

5x 1 ml DMF

The resulting imids of 6-bromo-1H-indazol-3-amine could be either isolated or converted to amides using terabutylammonium fluoride (0.5 M) in THF (16 hours).

The resins were then washed

5x 10% acetic acid in DCM

5x a) 1 ml DMF; b) 1 ml H_2O

5x a) 1 ml MeOH; b) 1 ml DCM

5x a) 1 ml DCM

The cleavage was performed in the following way:

1x 0.5 ml 20% TFA/DCM 5 min.

4x 0.2 ml 20% TFA/DCM 2 min.

The cleavage solutions were combined and then dried.

HPLC r.t. (Method I) 5.56; $[M-H]^+ = 354.1$

By working in an analogous way, starting from 6-bromo-1H-indazol-3-amine the following products were cleaved from the resin.

N-(6-bromo-1H-indazol-3-yl)-2,2,2-trifluoroethanesulfonamide

HPLC r.t. (Method I) 5.25; $[M+H]^+$= 359.89; $[M-H]^-$= 357.98

N-(6-bromo-1H-indazol-3-yl)-1-phenylmethanesulfonamide

HPLC r.t. (Method I) 6.0; $[M+H]^+$ = 367.93; $[M-H]^-$ = 366.04

N-(6-bromo-1H-indazol-3-yl)-1-[(1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonamide

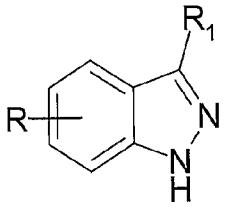
HPLC r.t. (Method I) 6.12; $[M+H]^+$ = 428.02; $[M-H]^-$= 426.13

4-acetyl-N-(6-bromo-1H-indazol-3-yl)benzenesulfonamide

HPLC r.t. (Method I) 6.12; $[M+H]^+$= 395, 436 $(M+1+MeCN)^+$

CLAIMS

1. A method for treating diseases caused by and/or associated with an altered protein kinase activity which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I)



(I)

wherein

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heteroatoms selected from S, O and N;

$\mathbf{R_1}$ is an optionally substituted group selected from -N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

$\mathbf{R_a}$ and $\mathbf{R_b}$ are, each independently, hydrogen or a straight or branched C_1-C_6 alkyl group;

R' and **R"** are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl or aryl C_1-C_6 alkyl wherein aryl is as above defined, or a 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl; or, when taken together with the nitrogen atom to which they are attached, R' and R" may form an optionally substituted 4 to 7 membered heterocycle, optionally containing an additional heteroatom selected from S, O or N;

or isomers, tautomers, carriers, prodrugs, and pharmaceutically acceptable salts thereof.

2. The method of claim 1 wherein the disease caused by and/or associated with an altered protein kinase activity is a cell proliferative disorder selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

3. The method of claim 2 wherein the cancer is selected from carcinoma, squamous cell carcinoma, hematopoietic tumors of lymphoid or myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma,

seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. The method of claim 1 wherein the cell proliferative disorder is selected from benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

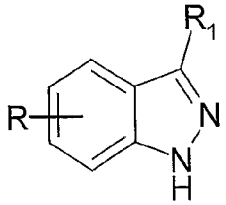
5. The method of claim 1 which provides tumor angiogenesis and metastasis inhibition.

6. The method of claim 1 further comprising subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

7. The method of claim 1 wherein the mammal in need thereof is a human.

8. A method for inhibiting protein kinase activity which comprises contacting the said kinase with an effective amount of a compound of formula (I) as defined in claim 1.

9. A compound of formula (I)



(I)

wherein

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heteroatoms selected from S, O and N;

$\mathbf{R_1}$ is an optionally substituted group selected from

-N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

$\mathbf{R_a}$ and $\mathbf{R_b}$ are, each independently, hydrogen or a straight or branched C_1-C_6 alkyl group;

R' and **R"** are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl or aryl C_1-C_6 alkyl wherein aryl is as above defined, or a 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl; or, when taken together with the nitrogen atom to which they are attached, R' and R" may form an optionally substituted 4

to 7 membered heterocycle, optionally containing an additional heteroatom selected from S, O or N;

or isomers, tautomers, carriers, prodrugs, and pharmaceutically acceptable salts thereof.

10. A compound of formula (I) according to claim 9 wherein R is an optionally substituted aryl group and R_1 is a group -NHCOR', wherein R' is as defined in claim 9.

11. A compound of formula (I) according to claim 9 wherein R is an optionally substituted aryl group and R_1 is a group -NHCONR'R", wherein one of R' or R" is a hydrogen atom and the remaining one of R' or R" is as defined in claim 9.

12. A compound of formula (I) according to claim 9 wherein R is an optionally substituted aryl group and R_1 is a group -NHCONR'R", wherein R' and R" are both, as defined in claim 9, other than hydrogen.

13. A compound of formula (I) according to claim 9 wherein R is in optionally substituted aryl group and R_1 is a group $-NHSO_2R'$, wherein R' is as defined in claim 9.

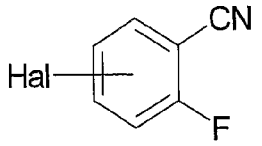
14. A compound of formula (I) according to claim 9 wherein R is in optionally substituted aryl group and R_1 is a group -NHCOOR', wherein R' is as defined in claim 9.

15. A compound of formula (I) according to claim 9 wherein R is in optionally substituted aryl group and R_1 is a group $-N=CH-NR_aR_b$, wherein R_a and R_b are both methyl groups.

16. A compound of formula (I) as defined in claim 9, optionally in the form of a pharmaceutically acceptable salt, selected from those listed in tables X and XI.

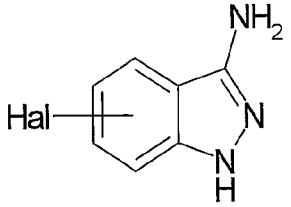
17. A process for preparing a compound of formula (I) and the pharmaceutically acceptable salts thereof, as defined in claim 9, which process comprises:

a) reacting a compound of formula (II) with hydrazine hydrate



(II)

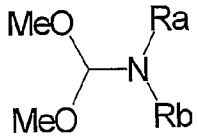
wherein Hal is a halogen atom, so as to obtain a compound of formula (III)



(III)

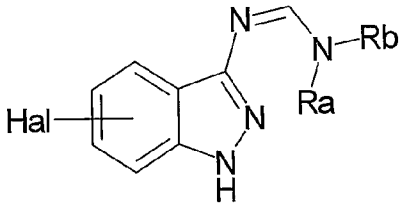
wherein the halogen atom is in position 5 or 6 of the indazole ring;

b) reacting the compound of formula (III) with a suitable dimethylacetal derivative of formula (IV)



(IV)

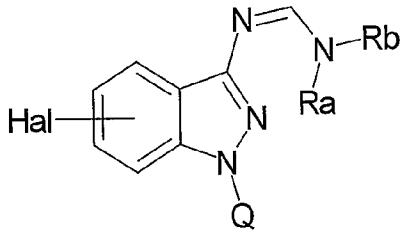
wherein R_a and R_b are as defined in claim 9, so as to obtain a compound of formula (I)



(I)

wherein R_a and R_b are as above defined; and, optionally, converting the thus obtained compound of formula (I) into another compound of formula (I), by:

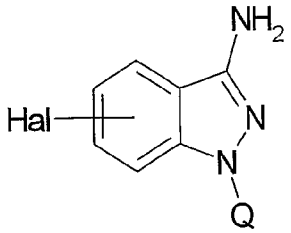
c) reacting the compound of formula (I), as per step (b) of the process, with a suitable indazole nitrogen protecting agent or, alternatively, supporting it onto a suitable polymeric resin so as to obtain a compound of formula (V)



(V)

wherein Q is the above nitrogen protecting group or represents the supporting resin;

d) reacting the compound of formula (V) with hydrazine monohydrate so as to get a compound of formula (VI)

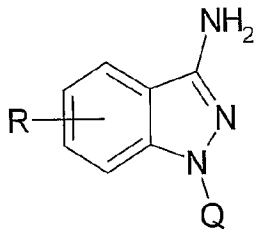


(VI)

e) reacting the compound of formula (VI) with a suitable boronic acid derivative of formula (VII)

$$R\text{-}B(OH)_2 \quad (VII)$$

wherein R is as defined in claim 9, so as to obtain a compound of formula (VIII)



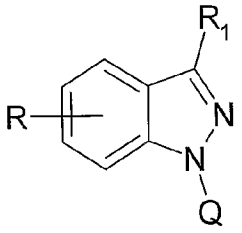
(VIII)

and reacting the compound of formula (VIII) according to any one of the alternative steps (f.1) or (f.2), as follows:

f.1) with any one of the compounds of formula (IX), (X), (XI) or (XII)

$$R'CO\text{-}Z \quad (IX) \qquad R'SO_2\text{-}Z \quad (X) \qquad R'\text{-}NCO \quad (XI) \qquad R'OCO\text{-}Z \quad (XII)$$

wherein R' is as defined in claim 9 and Z is a halogen atom or a suitable leaving group, so as to obtain the compounds of formula



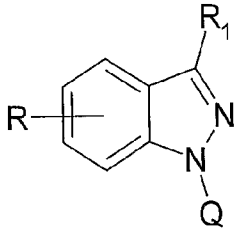
(XIII)

wherein R and Q are as above defined and R_1 is a group -NHCOR', $-NHSO_2R'$, -NHCONHR' or -NHCOOR'; or

f.2) with a suitable amine of formula (XIV)

$$HNR'R'' \quad (XIV)$$

wherein R' and R" are as defined in claim 9, in the presence of a suitable aryl chloroformate derivative, so as to obtain a compound of formula (XIII)



(XIII)

wherein R and Q are as above defined and R_1 is a group of formula -NHCONR'R";

g) deprotecting the compound of formula (XIII) being obtained according to any one of steps (f.1) or (f.2) or, alternatively, cleaving the polymeric resin so as to get the desired compound of formula (I) and, whenever desired, converting it into another compound of formula (I) and/or into a pharmaceutically acceptable salt thereof.

18. The process of claim 17 wherein, within the compound of formula (II) of step (a), Hal is a bromine atom.

19. The process of claim 17 wherein, within the compound of formula (IV) of step (b), R_a and R_b are both methyl groups.

20. The process of claim 17 wherein, in step (c), the compound of formula (I) is protected at the indazole nitrogen atom as tert-butoxy-carbonyl (BOC) group.

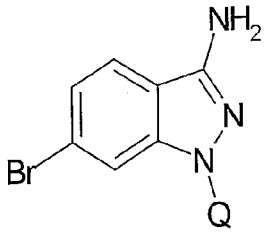
21. The process of claim 17 wherein, in step (c), the compound of formula (I) is supported onto a suitable polymeric resin comprising 2-chloro-trityl chloride resin, trityl chloride resin, p-nitrophenyl carbonate Wang resin or bromo-(4-methoxyphenyl)methyl polystyrene.

22. The process of claim 17 wherein, within the compounds of formula (IX), (X) or (XII) of step (f.1), Z represents a chlorine atom.

23. The process of claim 17 wherein, in step (f.2), the aryl chloroformate is selected from 4-nitrophenyl- or 4-chlorophenyl-chloroformate.

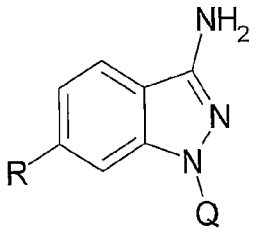
24. The process of claim 17 wherein, in step (g), the compound of formula (XIII) is deprotected at the indazole nitrogen atom or cleaved from the resin to which it is supported under acidic conditions, in the presence of hydrochloric or trifluoroacetic acid.

25. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the reacting the compound of formula (VIa)



(VIa)

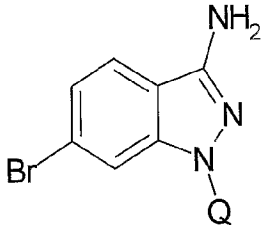
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

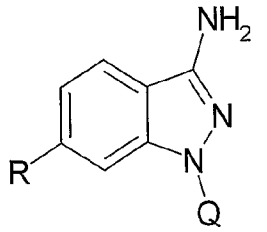
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (IX), as set forth in table II, and by subsequently operating as per step (g) of the process of claim 17.

26. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIa)



(VIa)

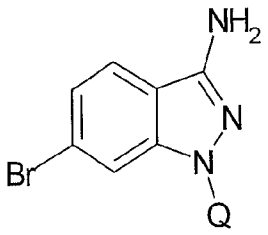
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

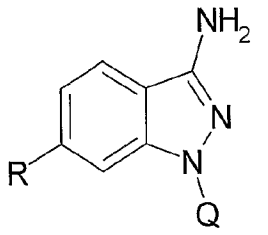
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (X), as set forth in table III, and by subsequently operating as per step (g) of the process of claim 17.

27. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIa)



(VIa)

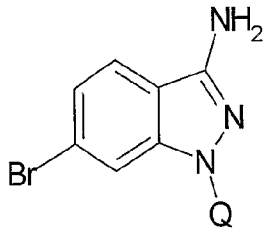
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

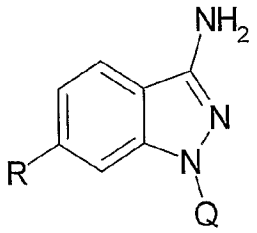
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (XI), as set forth in table IV, and by subsequently operating as per step (g) of the process of claim 17.

28. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIa)



(VIa)

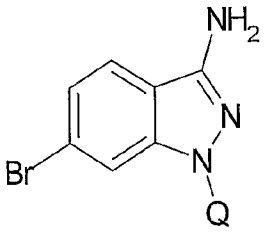
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

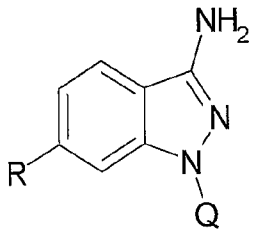
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (XII), as set forth in table V, and by subsequently operating as per step (g) of the process of claim 17.

29. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIa)



(VIa)

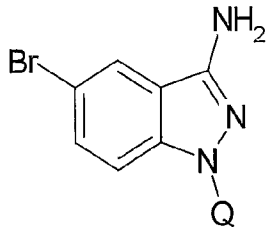
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIa)



(VIIIa)

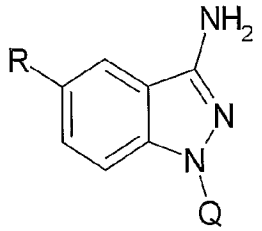
by then reacting each of the derivatives of formula (VIIIa) with each one of the derivatives of formula (XIV), as set forth in table VI, in the presence of 4-nitrophenyl-chloroformate, and by subsequently operating as per step (g) of the process of claim 17.

30. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIb)



(VIb)

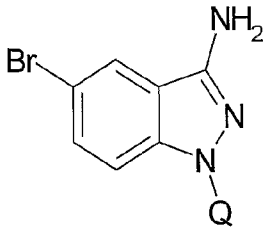
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

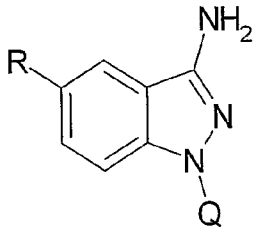
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (IX), as set forth in table II, and by subsequently operating as per step (g) of the process of claim 17.

31. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIb)



(VIb)

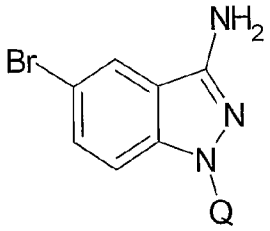
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

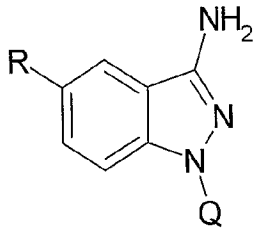
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (X), as set forth in table III, and by subsequently operating as per step (g) of the process of claim 17.

32. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIb)



(VIb)

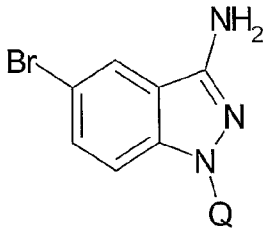
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

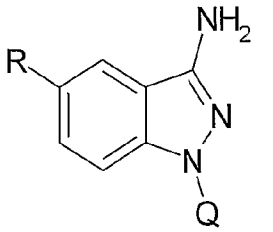
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (XI), as set forth in table IV, and by subsequently operating as per step (g) of the process of claim 17.

33. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIb)



(VIb)

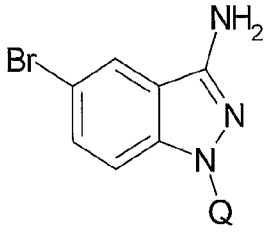
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

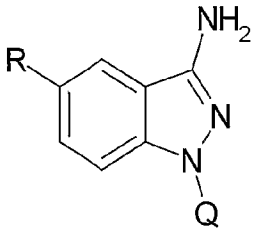
by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (XII), as set forth in table V, and by subsequently operating as per step (g) of the process of claim 17.

34. A compound of formula (I) according to claim 9, or a pharmaceutically acceptable salt thereof, which is obtainable, for instance through a combinatorial chemistry technique according to claim 17, by first reacting the compound of formula (VIb)



(VIb)

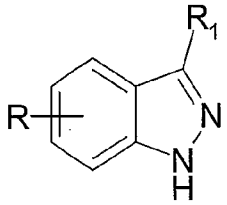
wherein Q is the supporting resin (Trityl-chloride resin) with each one of the derivatives of formula (VII), as set forth in table I, so as to obtain a plurality of compounds of formula (VIIIb)



(VIIIb)

by then reacting each of the derivatives of formula (VIIIb) with each one of the derivatives of formula (XIV), as set forth in table VI, in the presence of 4-nitrophenyl-chloroformate, and by subsequently operating as per step (g) of the process of claim 17.

35. A library of two or more compounds of formula (I)



(I)

wherein

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heteroatoms selected from S, O and N;

$\mathbf{R_1}$ is an optionally substituted group selected from

-N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

$\mathbf{R_a}$ and $\mathbf{R_b}$ are, each independently, hydrogen or a straight or branched C_1-C_6 alkyl group;

R' and **R"** are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl or aryl C_1-C_6 alkyl wherein aryl is as above defined, or a 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl; or, when taken together with the nitrogen atom to which they are attached, R' and R" may form an optionally substituted 4 to 7 membered heterocycle, optionally containing an additional heteroatom selected from S, O or N;

or isomers, tautomers, carriers, prodrugs, and pharmaceutically acceptable salts thereof.

36. A pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined in claim 9 and, at least, one pharmaceutically acceptable excipient, carrier or diluent.

37. A pharmaceutical composition according to claim 36 further comprising one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

38. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 9, for use as a medicament.

39. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 9, in the manufacture of a medicament for treating diseases caused by and/or associated with an altered protein kinase activity.

40. Use according to claim 39 wherein the disease caused by and/or associated with an altered protein kinase activity is tumor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04862

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/56 A61K31/416

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 32111 A (BAYER CORP) 1 July 1999 (1999-07-01) cited in the application page 6, line 11 - page 7, line 17; page 103, example 299, 25-34, 36, 38-40	1-5,7-9
A	WO 02 12242 A (PHARMACIA UPJOHN SPA) 14 February 2002 (2002-02-14) claims 1, 10-27	1-9,17, 35-40
A	WO 01 12188 A (PHARMACIA UPJOHN SPA ET AL) 22 February 2001 (2001-02-22) claims	1-9,17, 36-40

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2003	19/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 051847 A (SMITHKLINE BEECHAM PLC) 26 June 2003 (2003-06-26) page 5, line 4 - page 6, line 16; examples 1-4; table 1	1,2, 7-10,16, 25-34, 36,38,39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/04862

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/04862

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9932111 A	01-07-1999	AU 739642 B2	18-10-2001
		AU 1997199 A	12-07-1999
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